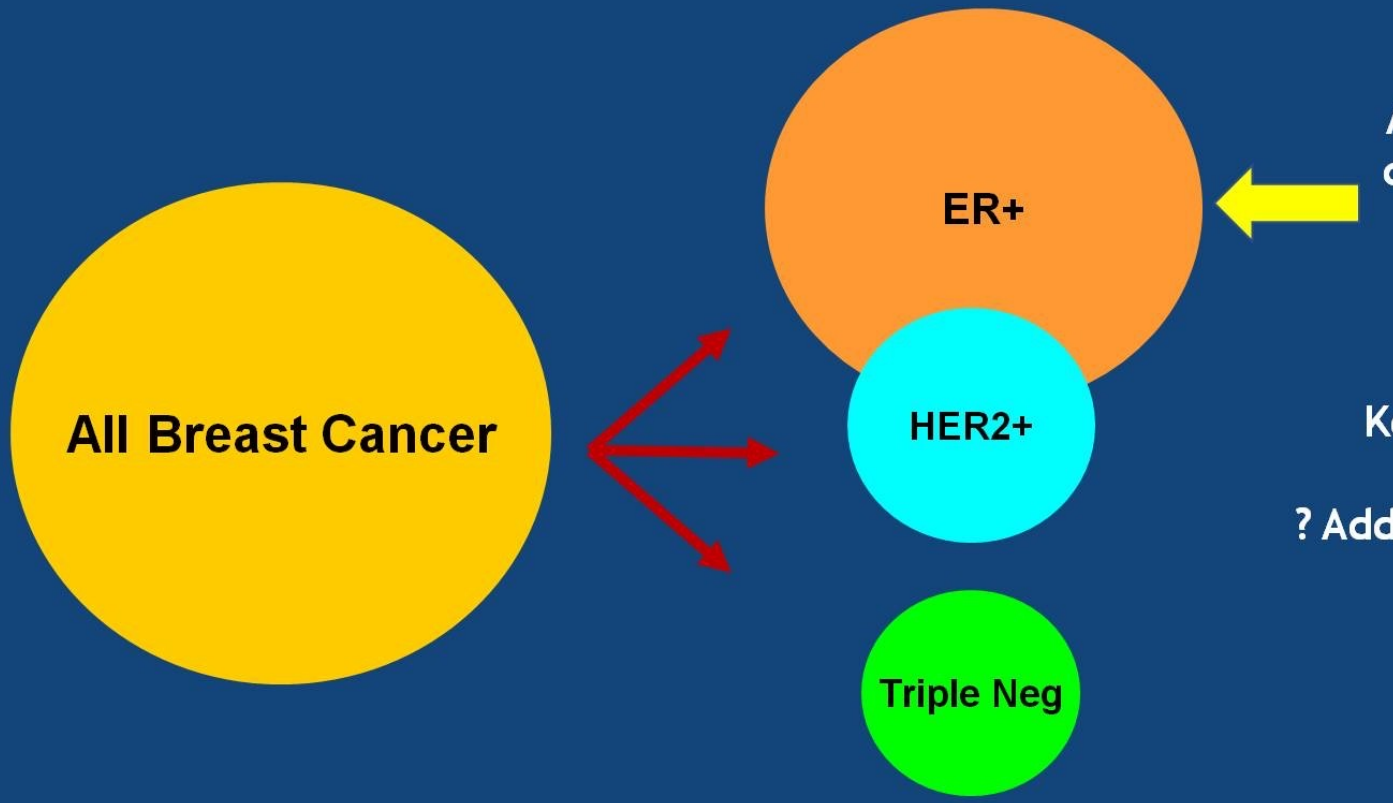
17ème Congrès International de Gynécologie - Obstétrique et Reproduction de la Côte d'Azur – Programme final
26 au 28 juin 2019 – Palais des congrès d'Antibes – Juan Les Pins

DOIT-ON UTILISER UN TEST GENOMIQUE POUR NOTRE DECISION THERAPEUTIQUE DANS LES CANCERS DU SEIN ADJUVANT RH + ANTIBES 2019

PH DALIVOUST

MARSEILLE HOPITAL EUROPEEN

Breast Cancer Clinical Subsets



About 50% of breast cancers are ER+ and HER2- and node-negative

Key Rx = endocrine

? Added benefit of chemo?

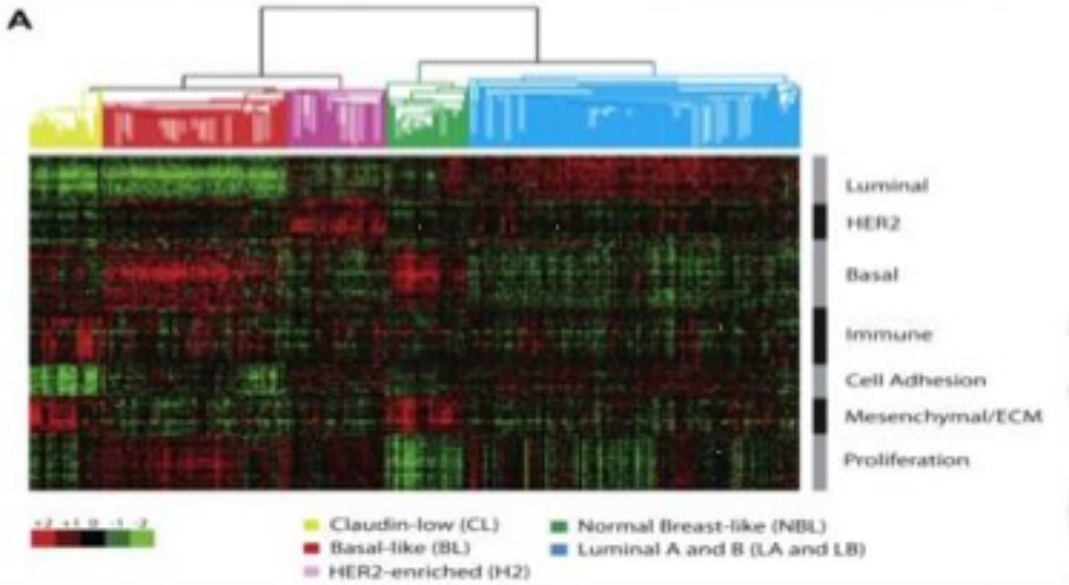
VALEUR PRONOSTIQUE DES SOUS TYPES MOLECULAIRES DES CANCERS DU SEIN

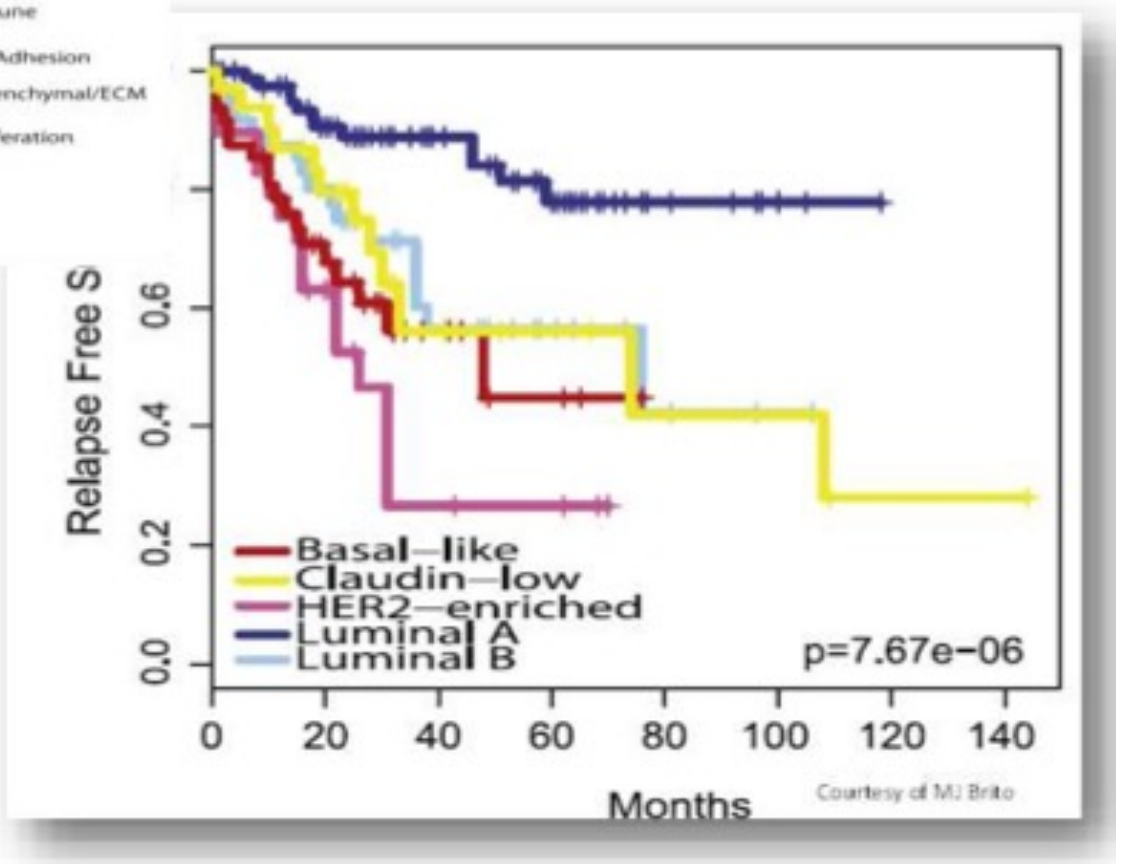
Breast Cancer Research

RESEARCH ARTICLE Open Access

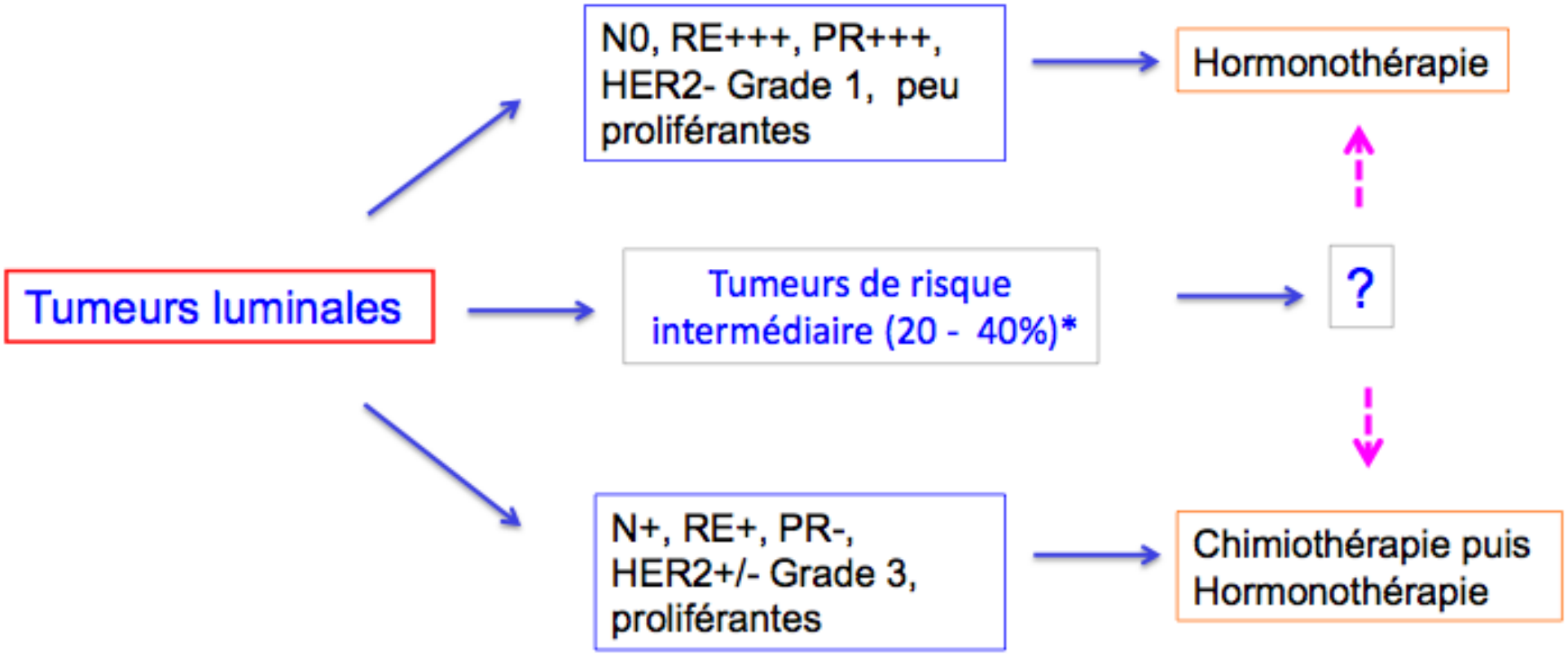
Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer

Alex Prat[1,2,3], Joel S Parker[1,4], Olga Karginova[1,2,3], Cheng Fan[1], Chad Livasy[1,5], Jason I Herschkowitz[6], Xiaping He[1,2,3], Charles M Perou[1,2,3]





DEFINITION CLINICO/PATHO DES TUMEURS LUMINALES



* 39%, Carlson JJ & Roth JA, 2013

Cancers du sein:
Facteurs pronostiques et prédictifs

Pronostic

- **Statut ganglionnaire**
- **Type histologique/grade**
- **Taille tumorale**
- **Age**
- **Embols Lymphatiques/Vasculaires**
- **Récepteurs hormonaux ER/PR**
- **HER2 *neu***
- **Signatures moléculaires**

Predictif

- **Récepteurs hormonaux ER/PR**
- **HER2 *neu***
- **Signatures moléculaires**

Ces facteurs peuvent être utilisés pour estimer un risque de récidive

Ces facteurs peuvent être utilisés pour estimer le bénéfice d'un traitement

- Adjuvant chemotherapy reduces recurrence in ER-positive, node-negative breast cancer

- U.S. N.I.H consensus panel in 2000 concluded *"…adjuvant ..chemotherapy … should be recommended to the majority of women with localized breast cancer regardless of lymph node, menopausal, or … receptor status."*

EFFICACY OF ADJUVANT CHEMOTHERAPY IN HIGH-RISK NODE-NEGATIVE BREAST CANCER

An Intergroup Study

EDWARD G. MANSOUR, M.D., ROBERT GRAY, PH.D., AHMAD H. SHATILA, M.D., C.K. OSBORNE, M.D., DOUGLASS C. TORMEY, M.D., PH.D., KENNEDY W. GILCHRIST, M.D., M. ROBERT COOPER, M.D., AND GEOFFREY FALKSON, M.D.

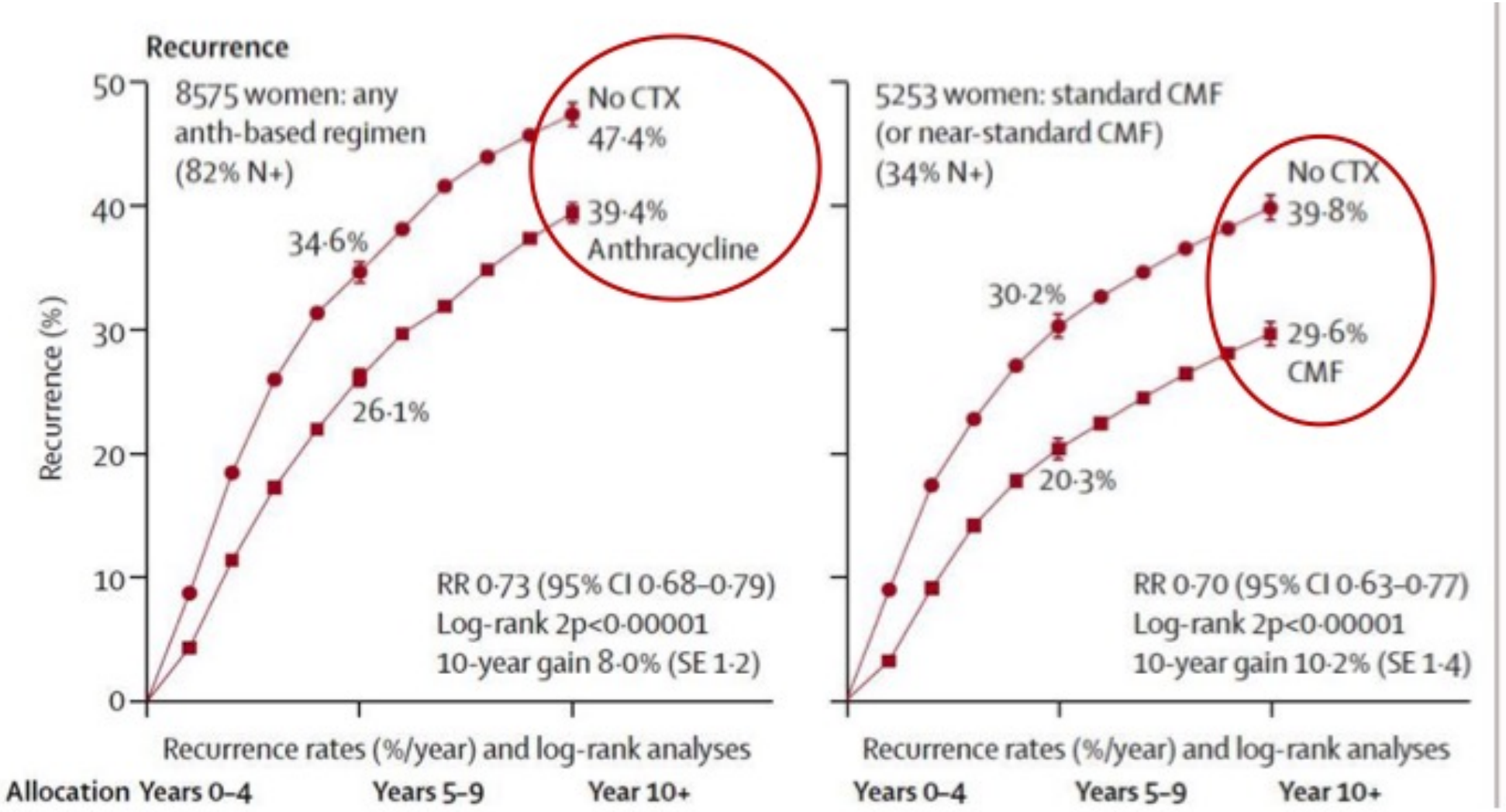
Mansour et al. *N Eng J Med* 1989; 320:485-490; *JNCI* 2001; 93: 979–989

SPECIAL ARTICLE

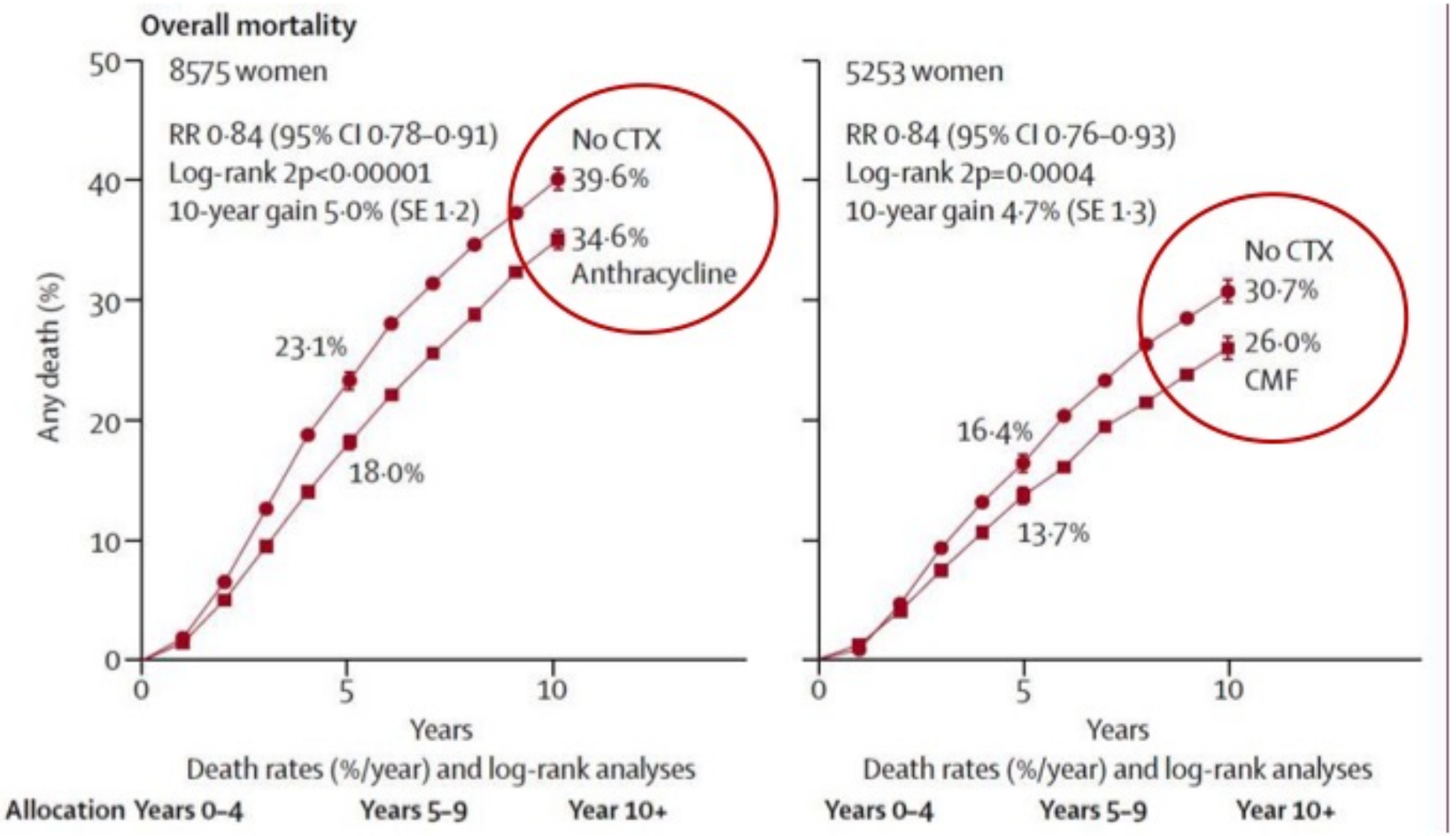
National Institutes of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1–3, 2000

*National Institutes of Health Consensus Development Panel**

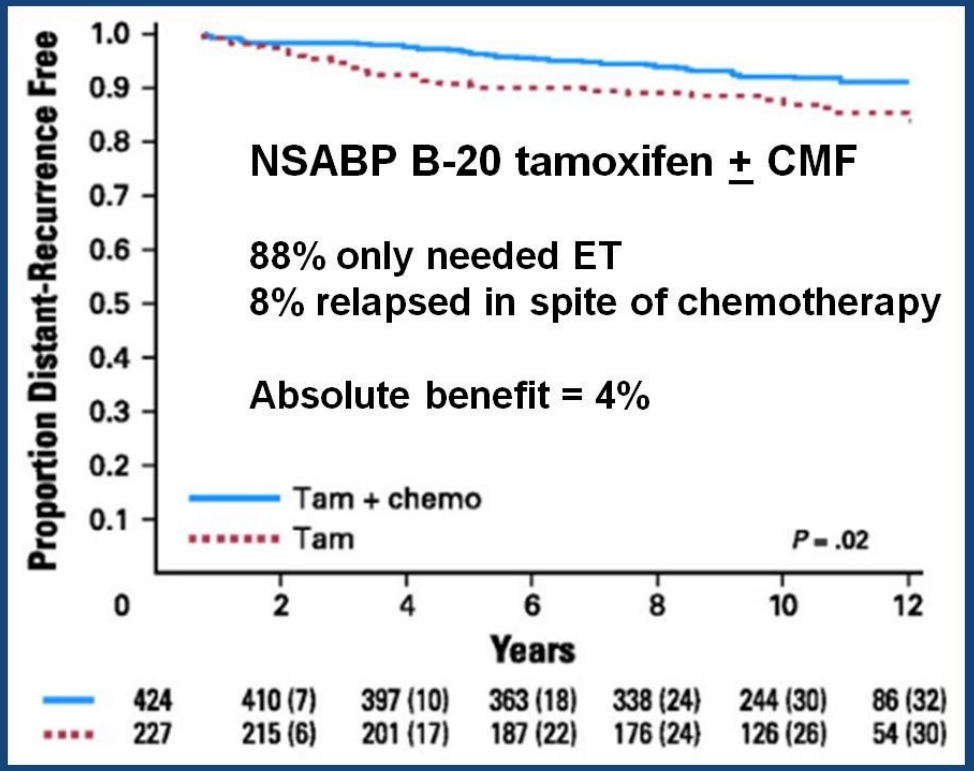
META ANALYSE DE PETO EBCTG 2011



META ANALYSE DE PETO EBCTG 2011



The Problem of Overtreatment



Paik et al. J Clin Oncol 2006

Early 2000s:

Most ER+ node-negative breast cancer patients received chemo

Most did not benefit

Chiffres

- Environ 50 000 nouveau cas en France *[Inca]*
- 60% de chimiothérapie adjuvante en cas de cancer du sein ER+ *[Chereau et al 2011; Fekih et al 2014]* : **30 000 chimiothérapies**
- 4-5% de bénéfice de la chimiothérapie adjuvante *[Chereau et al 2011]*

28500 chimiothérapies sans effet

MALGRE PLUS DE QUINZE ANS D'EFFORTS ET DE RECHERCHE TOUJOURS DES CONTROVERSES

QUI PEUT ETRE EPARGNÉ D'UNE CHIMIOTHÉRAPIE !

QUI N'A PAS BESOIN DE PROLONGER L' HORMONOTHERAPIE AU DELA DE 5 ANS !

DECISION D'UN TRAITEMENT ADJUVANT

NEVER FORGET THAT…

The « low-enough » risk that justifies treatment de-escalation… is a patient's decision!

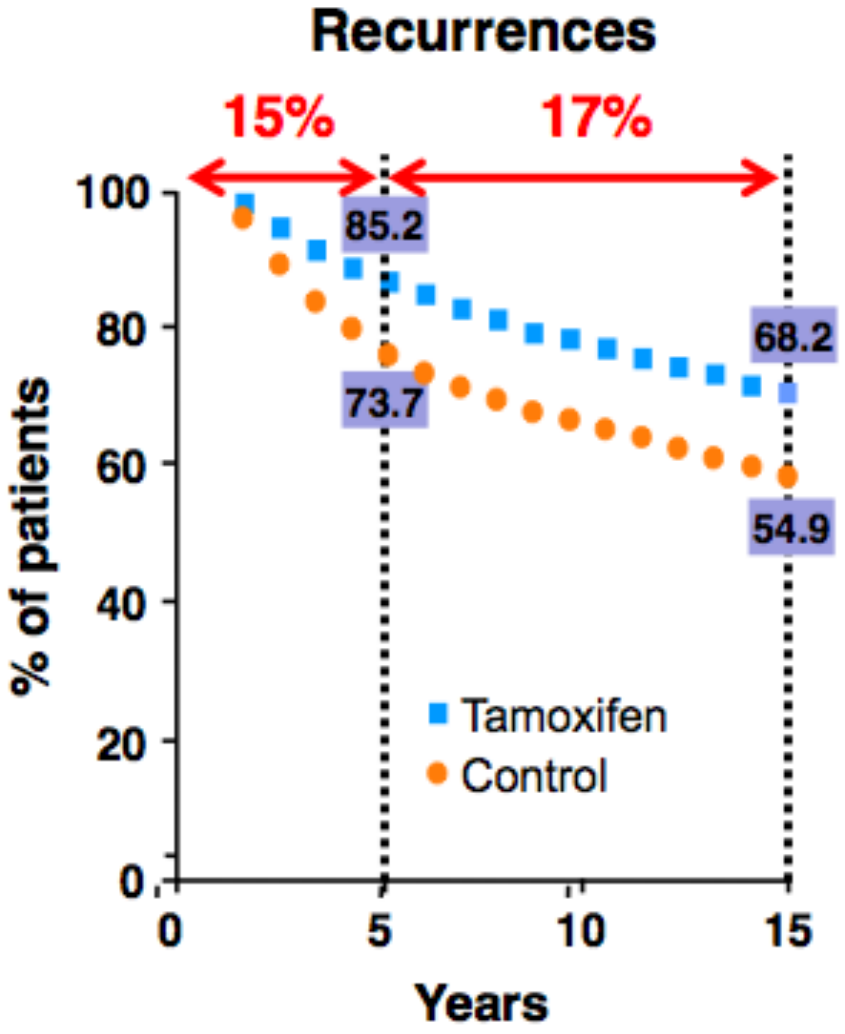
« High risk » does not mean that the treatment will work!

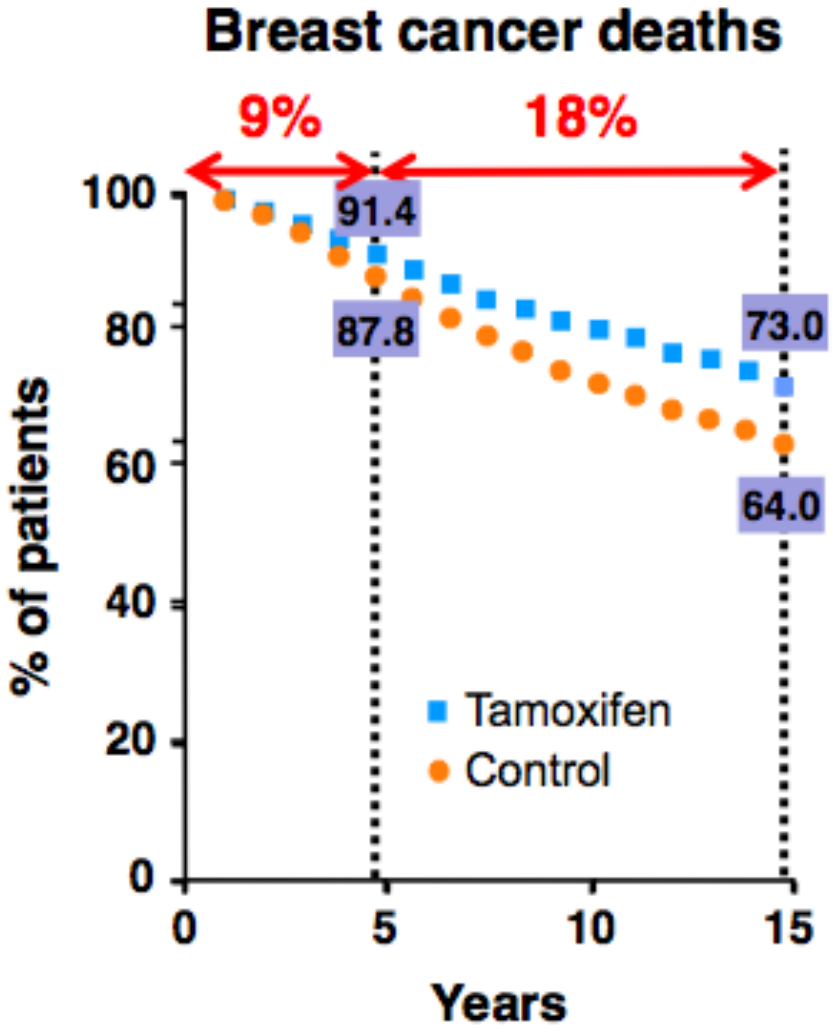
DECISION D'UN TRAITEMENT ADJUVANT

NEVER FORGET THAT…

The « history » of luminal BC extends beyond 5 years, with late relapses seen particularly if large T a/o N+

More than Half of all Breast Cancer Recurrences and Deaths Occur Post- 5y Tamoxifen





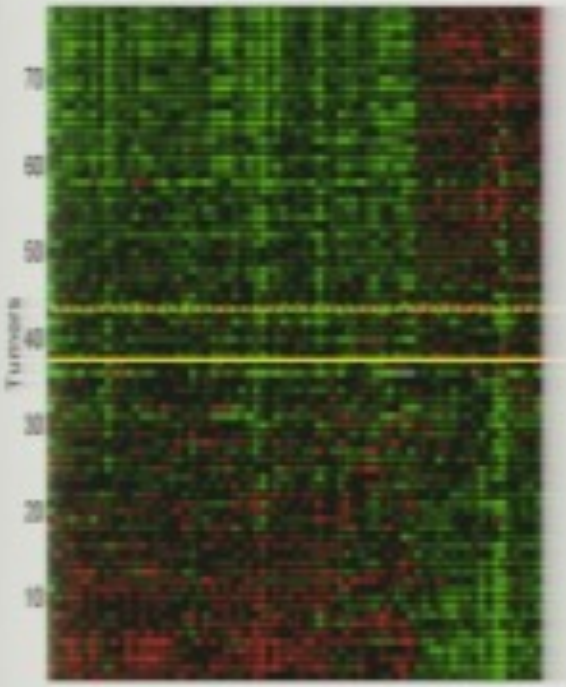
EBCTCG, Lancet. 2005

Signatures disponibles

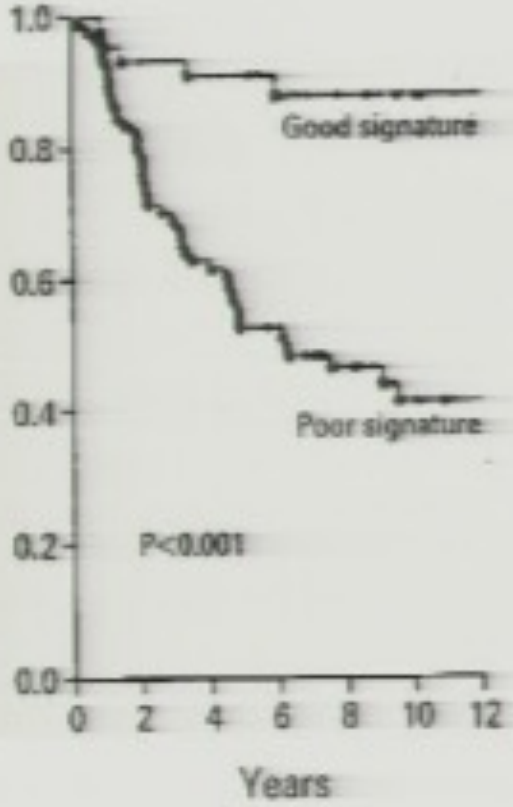
- Oncotype
- Endopredict
- Mammaprint
- Prosigna

Improved risk assessment of early breast cancer through gene expression profiling

Microarray



Gene-expression profile



Good signature

~4% die of breast cancer
~96% survive breast cancer

Poor signature

~50% die of breast cancer
~50% survive breast cancer

Supported by the EU framework VI programme

N Engl J Med, Vol 347 (25), Dec. 2002

The New England
Journal of Medicine

VOLUME 347 DECEMBER 19, 2002 NUMBER 25

A GENE-EXPRESSION SIGNATURE AS A PREDICTOR OF SURVIVAL IN BREAST CANCER

MARC J. VAN DE VIJVER, M.D., PH.D., YUDONG D. HE, PH.D., LAURA J. VAN 'T VEER, PH.D., HONGYUE DAI, PH.D., AUGUSTINUS A.M. HART, M.SC., DOREN W. VOSKUIL, PH.D., GEORGE J. SCHREIBER, M.SC., JOHANNES L. PETERSE, M.D., CHRIS ROBERTS, PH.D., MATTHEW J. MARTON, PH.D., MARK PARRISH, DOUWE ATSMA, ANKE WITTEVEEN, ANNUSKA GLAS, PH.D., LEONIE DELAHAYE, TONY VAN DER VELDE, HARRY BARTELINK, M.D., PH.D., SJOERD RODENHUIS, M.D., PH.D., EMIEL T. RUTGERS, M.D., PH.D., STEPHEN H. FRIEND, M.D., PH.D., AND RENE BERNARDS, PH.D.

ABSTRACT

Background A more accurate means of prognostication in breast cancer will improve the selection of patients for adjuvant systemic therapy.

Methods Using microarray analysis to evaluate our previously established 70-gene prognosis profile, we classified a series of 295 consecutive patients with primary breast carcinomas as having a gene-expression signature associated with either a poor prognosis or a good prognosis. All patients had stage I or II breast cancer and were younger than 53 years old; 151 had lymph-node–negative disease, and 144 had lymph-node–positive disease. We evaluated the predictive power of the prognosis profile using univariable and multivariable statistical analyses.

Results Among the 295 patients, 180 had a poor-prognosis signature and 115 had a good-prognosis signature, and the mean (±SE) overall 10-year survival rates were 54.6±4.4 percent and 84.5±2.6 percent, respectively. At 10 years, the probability of remaining free of distant metastases was 50.8±4.5 percent in the group with a poor-prognosis signature and 85.2±4.3 percent in the group with a good-prognosis signature. The estimated hazard ratio for distant metastases in the group with a poor-prognosis signature, as compared with the group with the good-prognosis signature, was 5.1 (95 percent confidence interval, 2.9 to 9.0; P<0.001). This ratio remained significant when the groups were analyzed according to lymph-node status. Multivariable Cox regression analysis showed that the prognosis profile was a strong independent factor in predicting disease outcome.

Conclusions The gene-expression profile we studied is a more powerful predictor of the outcome of disease in young patients with breast cancer than standard systems based on clinical and histologic criteria. (N Engl J Med 2002;347:1999-2009.)

ADJUVANT systemic therapy substantially improves disease-free and overall survival in both premenopausal and postmenopausal women up to the age of 70 years with lymph-node–negative or lymph-node–positive breast cancer.[1,2] It is generally agreed that patients with poor prognostic features benefit the most from adjuvant therapy.[3,4] The main prognostic factors in breast cancer are age, tumor size, status of axillary lymph nodes, histologic type of the tumor, pathological grade, and hormone-receptor status. A large number of other factors have been investigated for their potential to predict the outcome of disease, but in general, they have only limited predictive power.[5]

Using complementary DNA (cDNA) microarrays to analyze breast-cancer tissue, Perou et al. identified tumors with distinct patterns of gene expression that they termed "basal type" and "luminal type."[6] These subgroups differ with respect to the outcome of disease in patients with locally advanced breast cancer.[7] In addition, microarray analysis has been used to distinguish cancers associated with *BRCA1* or *BRCA2* mutations[8,9] and to determine estrogen-receptor status[6,9,10] and lymph-node status.[11,12]

Using inkjet-synthesized oligonucleotide microarrays, we recently identified a gene-expression profile

From the Division of Diagnostic Oncology (M.J.V., L.J.V., D.W.V., H.L.P., D.A., A.W., A.G., L.D.), Radiotherapy (A.A.M.H., H.B.), Medical Oncology (S.R.), Biometrics (D.V.), Surgical Oncology (E.T.R.), and Molecular Carcinogenesis (R.B.), Netherlands Cancer Institute, Amsterdam; the Center for Biomedical Genetics, Amsterdam (R.B.); and Rosetta Inpharmatics, Kirkland, Wash. (Y.D.H., H.D., G.J.S., C.R., M.J.M., M.P., S.H.F.). Address reprint requests to Dr. Bernards at the Division of Molecular Carcinogenesis, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands, or at r.bernards@nki.nl.

Drs. van de Vijver, He, and van 't Veer contributed equally to this article.

First validation:

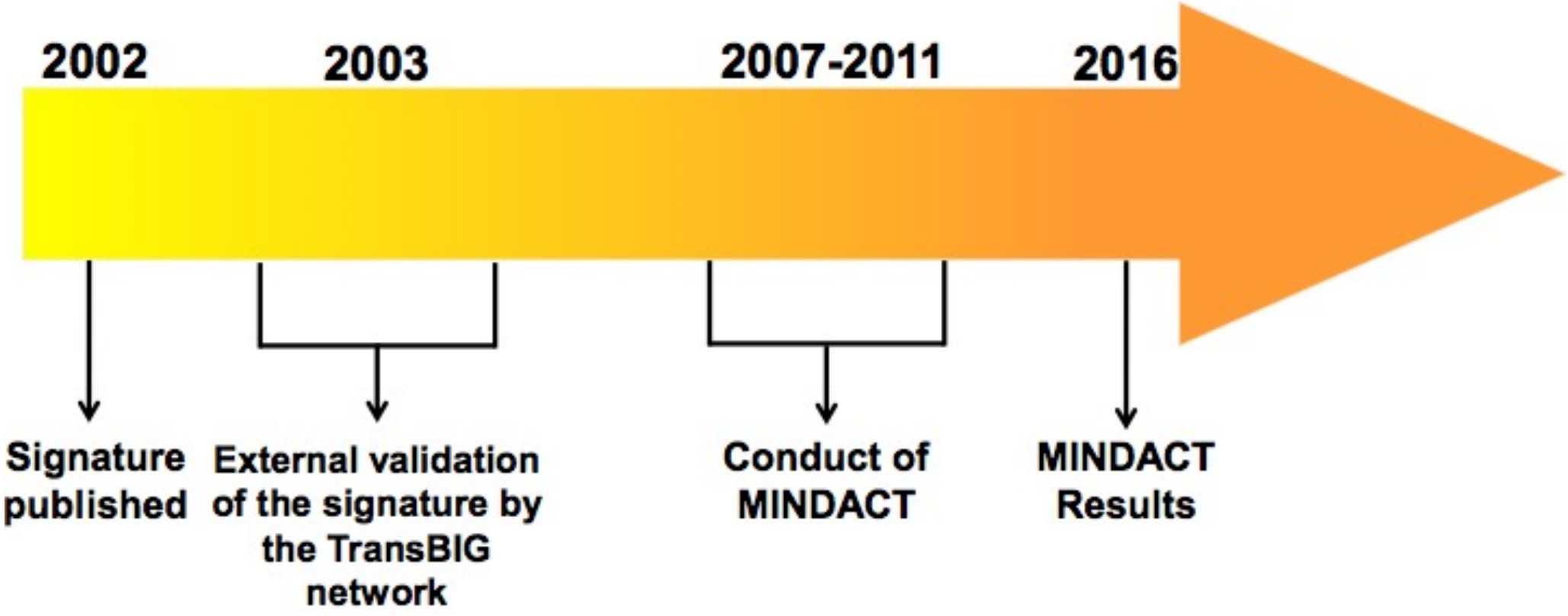
Van de Vijver et al. (2002)

New England J. Med. **347**, 1999-2009.

295 patients

mammaprint
decoding breast cancer

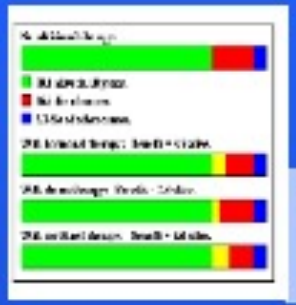
Validation of the MammaPrint® signature : 15 years of intensive collaborative work!



MINDACT TRIAL DESIGN

EORTC European Organisation for Research and Treatment of Cancer

TRANSBIG

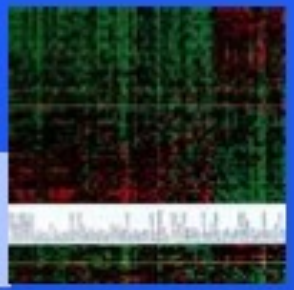


Registration & Screening
Surgery

N= 6600

Clinical-Pathological (C) risk
(Adjuvant! Online)

Genomic (G) risk
(70-gene signature)



C-high/ G-high

Discordant cases
C-high/G-low or C-low/G-high

C-low/G-low

1st randomization to treatment
use Clinical vs. Genomic risk

Chemotherapy

2nd randomization
Anthracycline –based vs. Capecitabine-Docetaxel

No Chemotherapy

HR+

Endocrine therapy

HR+

3rd randomization
Tamoxifen 2y / Letrozole 5y vs. Letrozole 7y

F. Cardoso et al, NEJM 2016

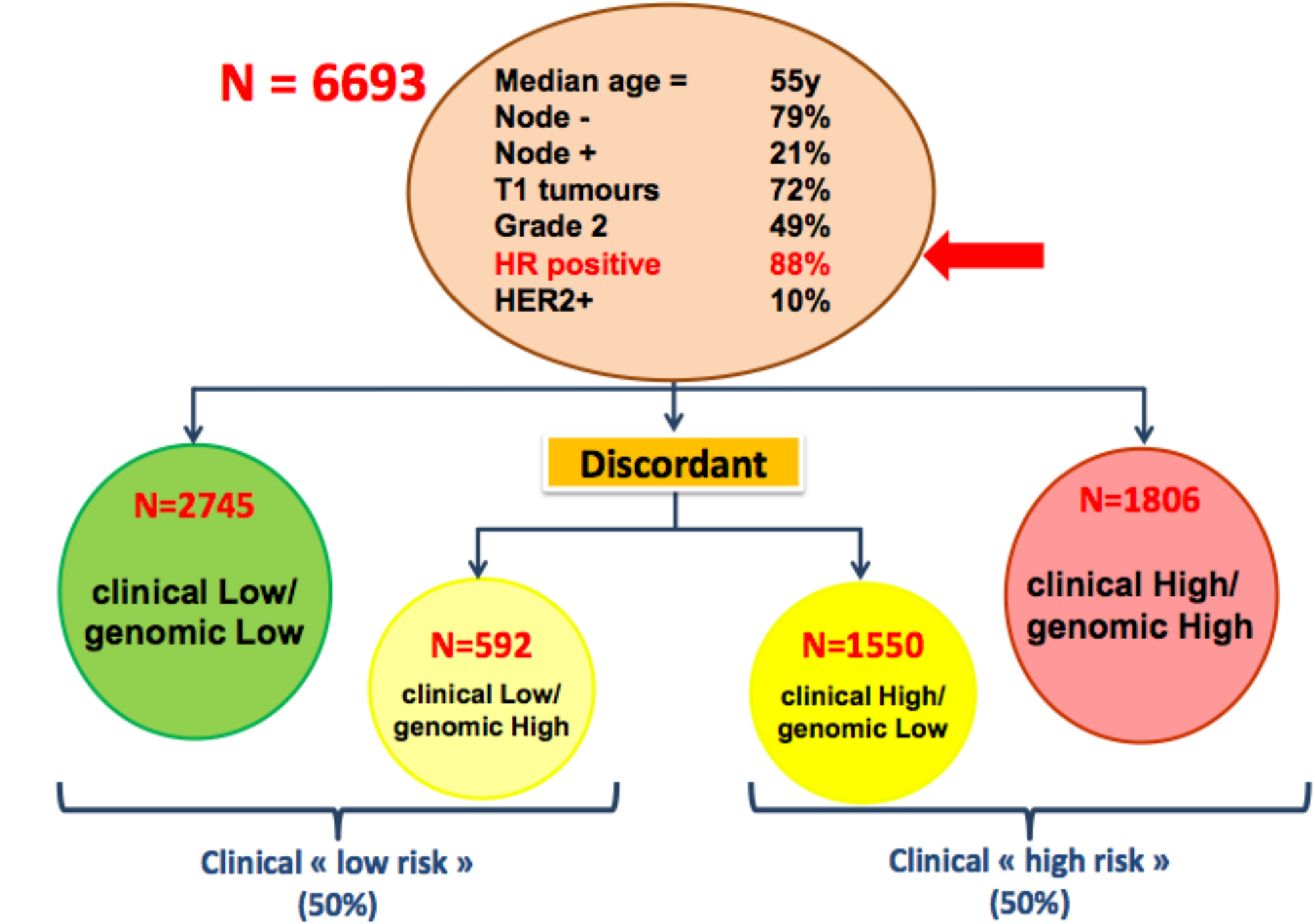
MammaPrint®
Low vs High genomic risk

Adj.! Online
Low vs High clinical risk

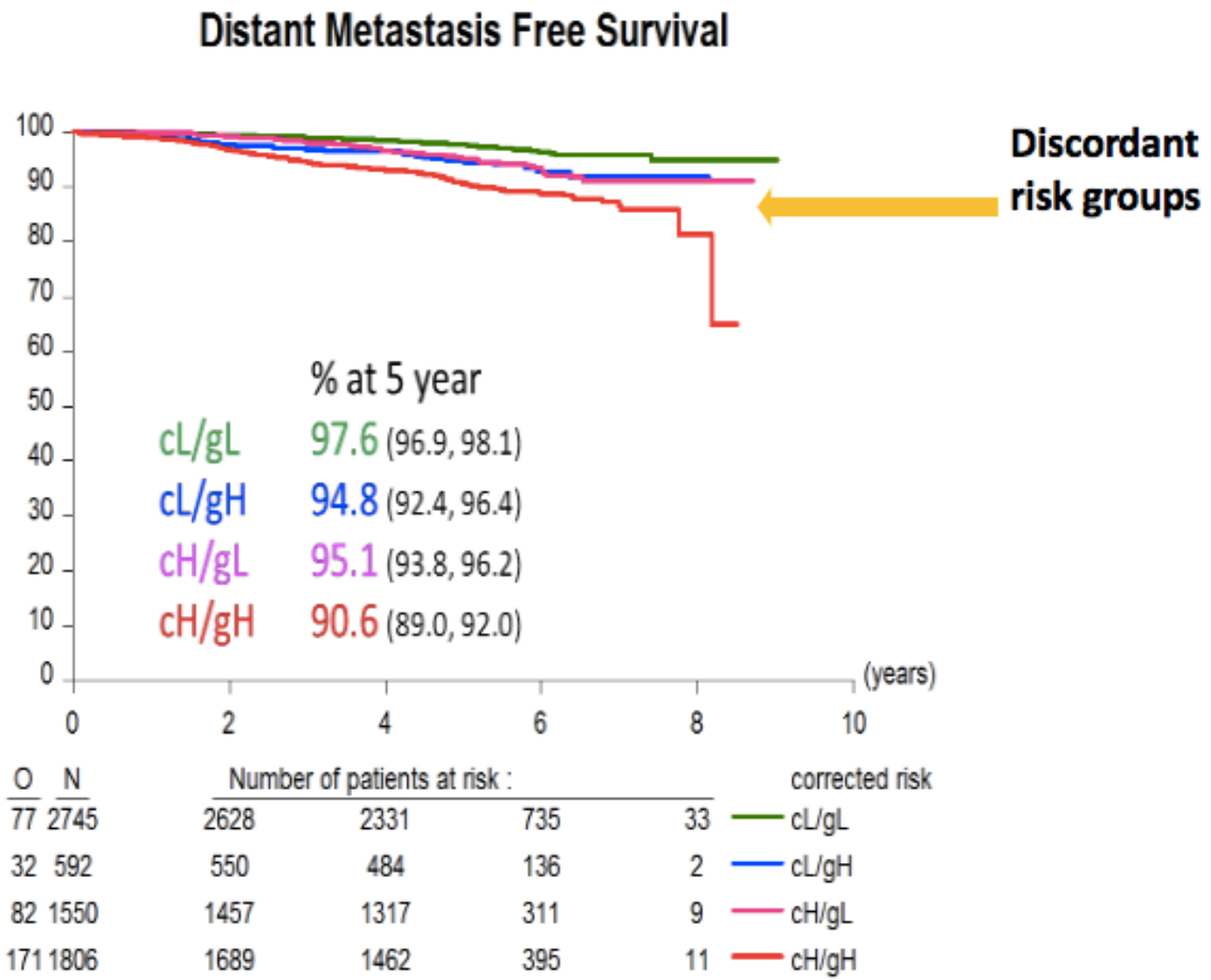
Hypothesis : the Genomic assay will outperform the Clinical criteria by reducing the prescription of adjuvant chemotherapy WITHOUT IMPAIRING OUTCOME

More specifically: clinically high risk patients with a low risk gene signature randomized not to receive CTX should have a 5 year DMFS of ≥ 92%

The MINDACT study: Patient demographics



DMFS MINDACT population at 5-year median follow-up



Clinical outcome of the MINDACT population at 5y median follow-up
DISCORDANT RISK GROUPS: PRIMARY TEST

The primary analysis population

Discordant risks

c-Low /g-High

c-High/g-Low

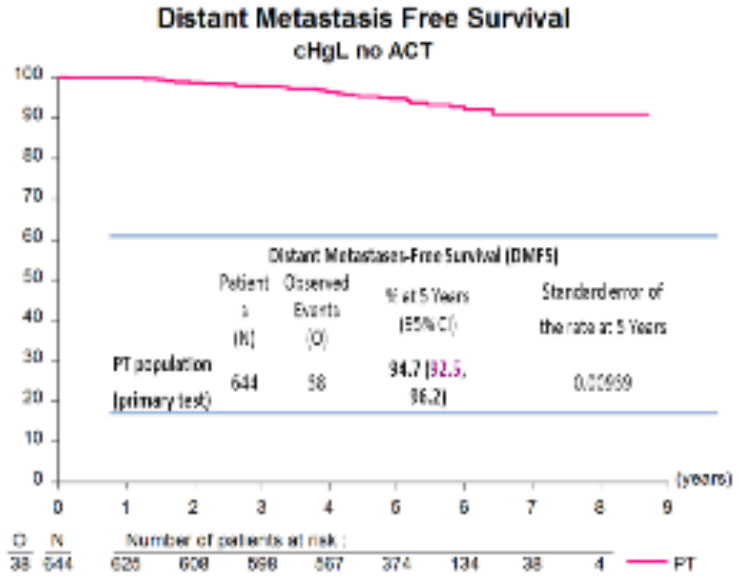
RANDOMIZATION

No chemotherapy N = 748

CT

No change in risk post enrollement and no CT received N = 644

The primary statistical test (DMFS at 5Y)

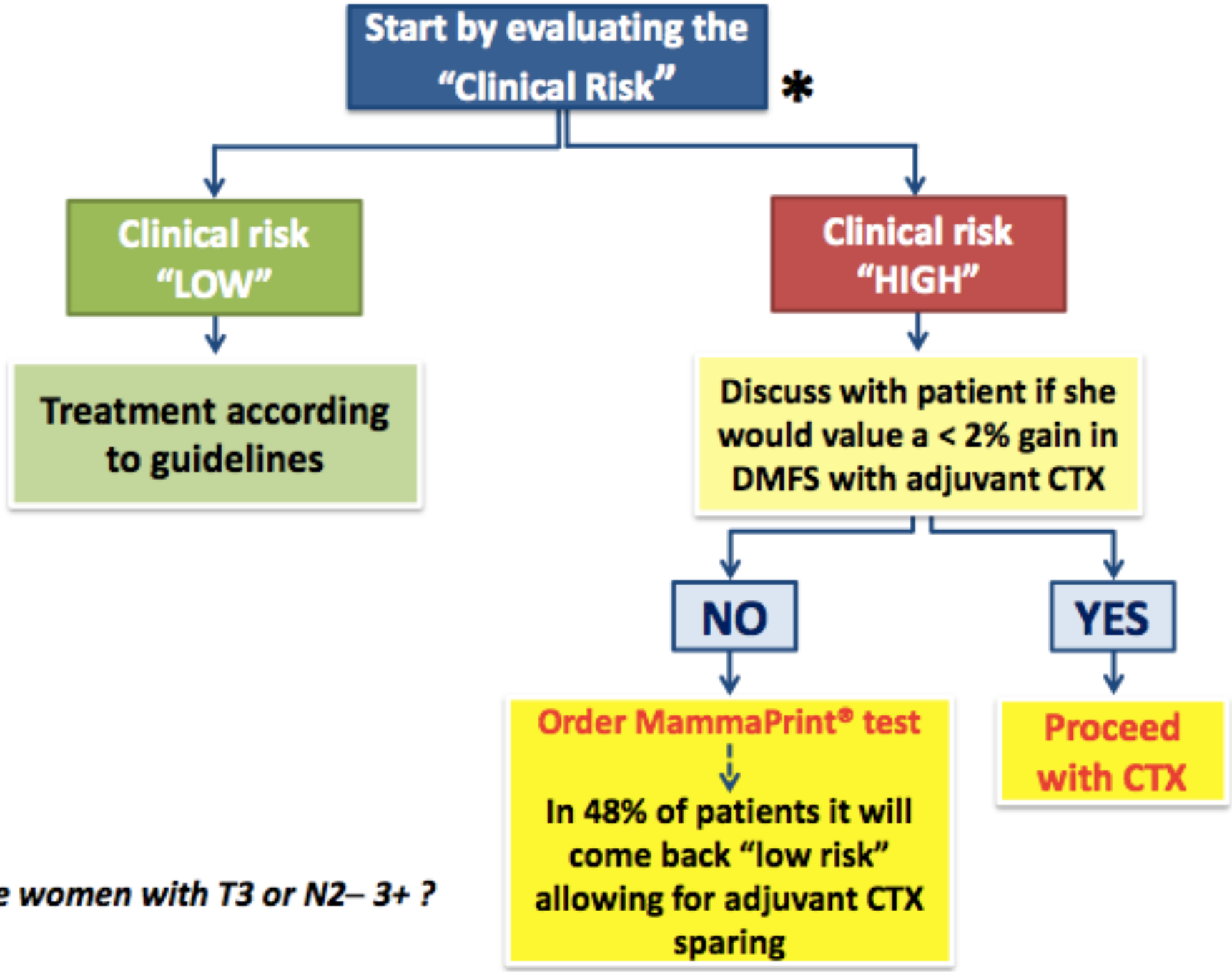


Null Hypothesis: set at 92%

Observed 5Y DMFS = 94.7%

95% CI ≈ 92.5 – 96.2% excludes 92% !!!

UTILISATION DE MAMMAPRINT EN PRATIQUE CLINIQUE



**Exclude women with T3 or N2– 3+ ?*

Conclusion MINDACT

- Preuve de niveau 1A d'une valeur de bon pronostic en l'absence de chimiothérapie
  - c-High/g-Low : SSR à 5 ans ~95%, (+1,5 % avec CT, non significatif)
  - c-low/g-high patients : SSR ~96% (+ 2,5 % avec CT, non significatif)
- Peut permettre une réduction de prescription de CT
  - Dans la population globale de 14%
  - Dans le groupe à haut risque clinique de 46%

Oncotype DX® 21-Gene Recurrence Score® (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

INVASION
Stromelysin 3
Cathepsin L2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

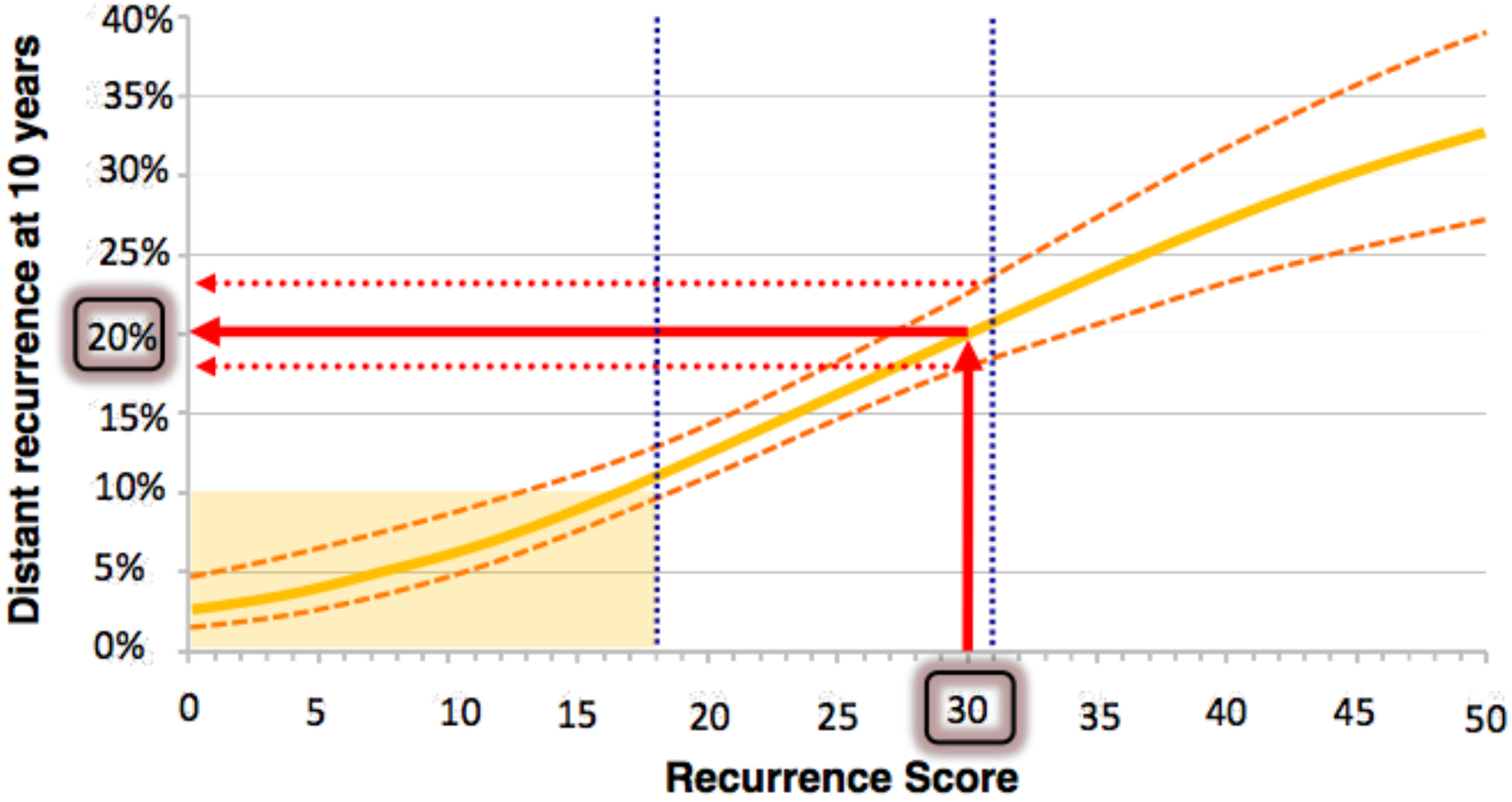
CD68

HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

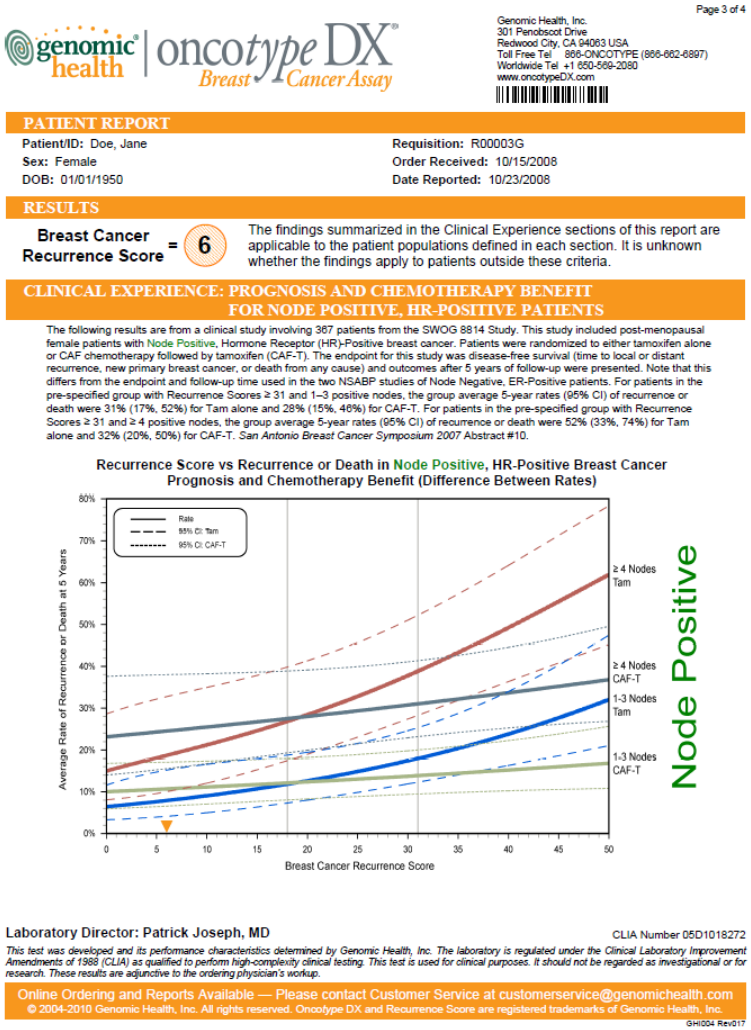
Paik et al. *N Engl J Med.* 2004;351: 2817-2826

Oncotype DX® result is a continuous prognostic indicator of recurrence risk



Paik NEJM 2004

Oncotype DX® Compte rendu



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genomic health | oncotype DX Breast Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063 USA
Toll Free Tel 866-ONCOTYPE (866-662-6897)
Worldwide Tel +1 650-569-2060
www.oncotypeDX.com

PATIENT REPORT

Patient/ID: Doe, Jane
Sex: Female
DOB: 01/01/1950

Requisition: R00003G
Order Received: 10/15/2008
Date Reported: 10/23/2008

RESULTS

Breast Cancer Recurrence Score = **6**

The findings summarized in the Clinical Experience sections of this report are applicable to the patient populations defined in each section. It is unknown whether the findings apply to patients outside these criteria.

CLINICAL EXPERIENCE: PROGNOSIS AND CHEMOTHERAPY BENEFIT FOR NODE POSITIVE, HR-POSITIVE PATIENTS

The following results are from a clinical study involving 367 patients from the SWOG 8814 Study. This study included post-menopausal female patients with Node Positive, Hormone Receptor (HR)-Positive breast cancer. Patients were randomized to either tamoxifen alone or CAF chemotherapy followed by tamoxifen (CAF-T). The endpoint for this study was disease-free survival (time to local or distant recurrence, new primary breast cancer, or death from any cause) and outcomes after 5 years of follow-up were presented. Note that this differs from the endpoint and follow-up time used in the two NSABP studies of Node Negative, ER-Positive patients. For patients in the pre-specified group with Recurrence Scores ≥ 31 and 1–3 positive nodes, the group average 5-year rates (95% CI) of recurrence or death were 31% (17%, 52%) for Tam alone and 28% (15%, 46%) for CAF-T. For patients in the pre-specified group with Recurrence Scores ≥ 31 and ≥ 4 positive nodes, the group average 5-year rates (95% CI) of recurrence or death were 52% (33%, 74%) for Tam alone and 32% (20%, 50%) for CAF-T. *San Antonio Breast Cancer Symposium 2007* Abstract #10.

Recurrence Score vs Recurrence or Death in Node Positive, HR-Positive Breast Cancer
Prognosis and Chemotherapy Benefit (Difference Between Rates)

Laboratory Director: Patrick Joseph, MD
CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

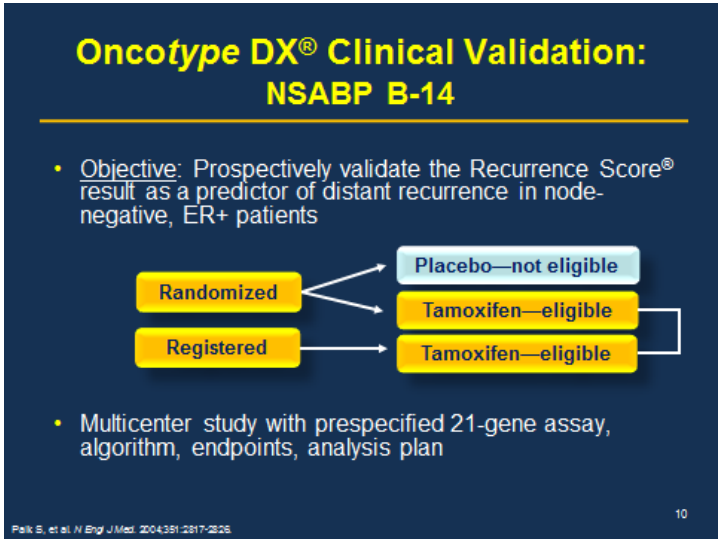
Online Ordering and Reports Available — Please contact Customer Service at customerservice@genomichealth.com

GHI004 Rev017

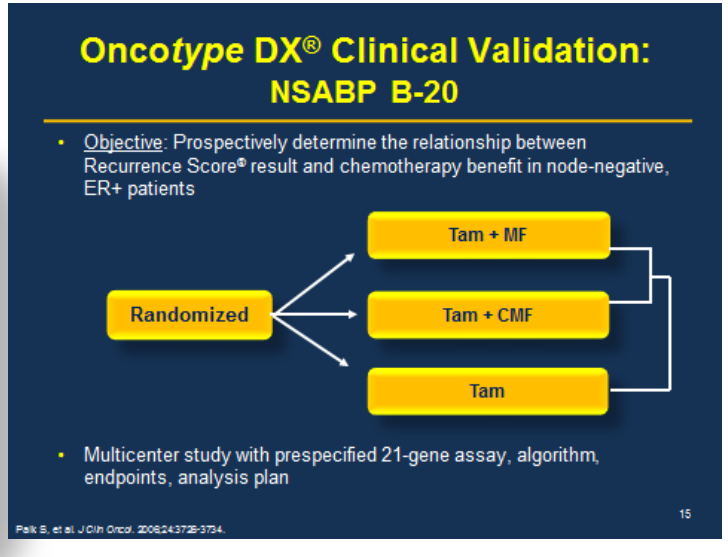
- Le compte rendu Oncotype DX fournit les informations sur
  - Le pronostic
  - Le bénéfice prédictif de la chimiothérapie
  - Des données quantitatives sur ER / PR / HER2
- Pour les N+, le compte-rendu comprend une page spécifique d'informations prédictives et pronostiques

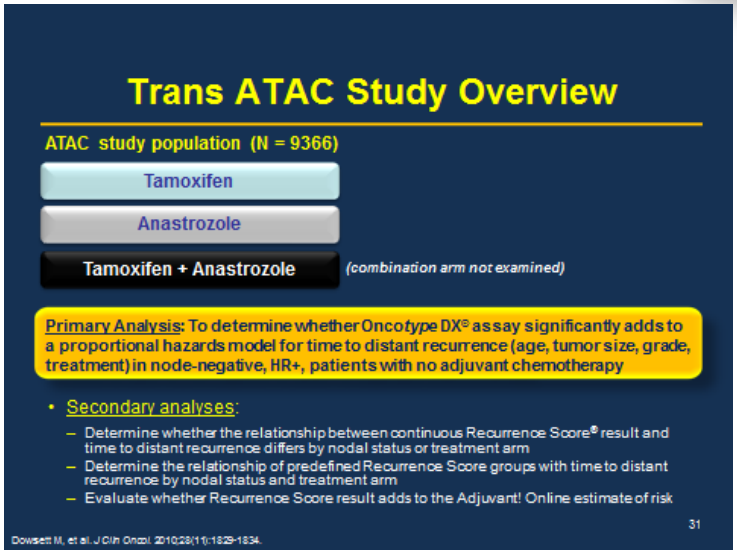
Validation du test génomique Oncotype Dx®

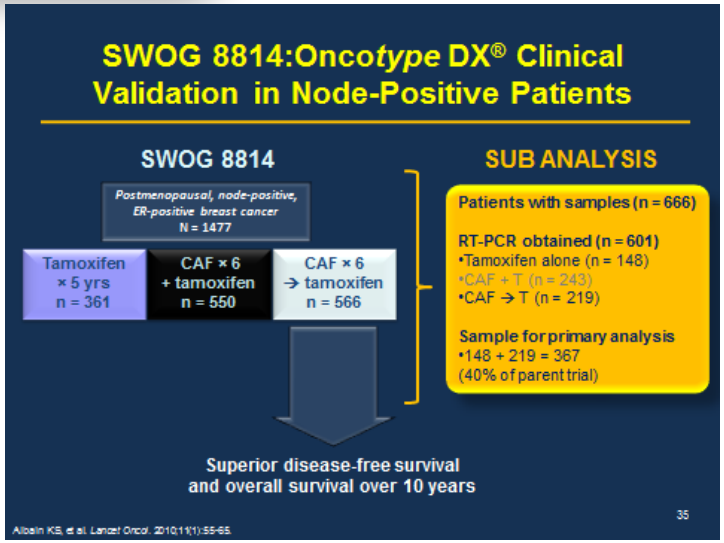
- A partir des données d'études randomisées par des groupes coopérateurs sur des populations homogènes de patientes.
- 13 études dont 6 randomisées : > 5,700 patientes (>3,400 N- et >2,080 N+)



Pronostic pour la récidive métastatique et predictif pour le bénéfice du traitement

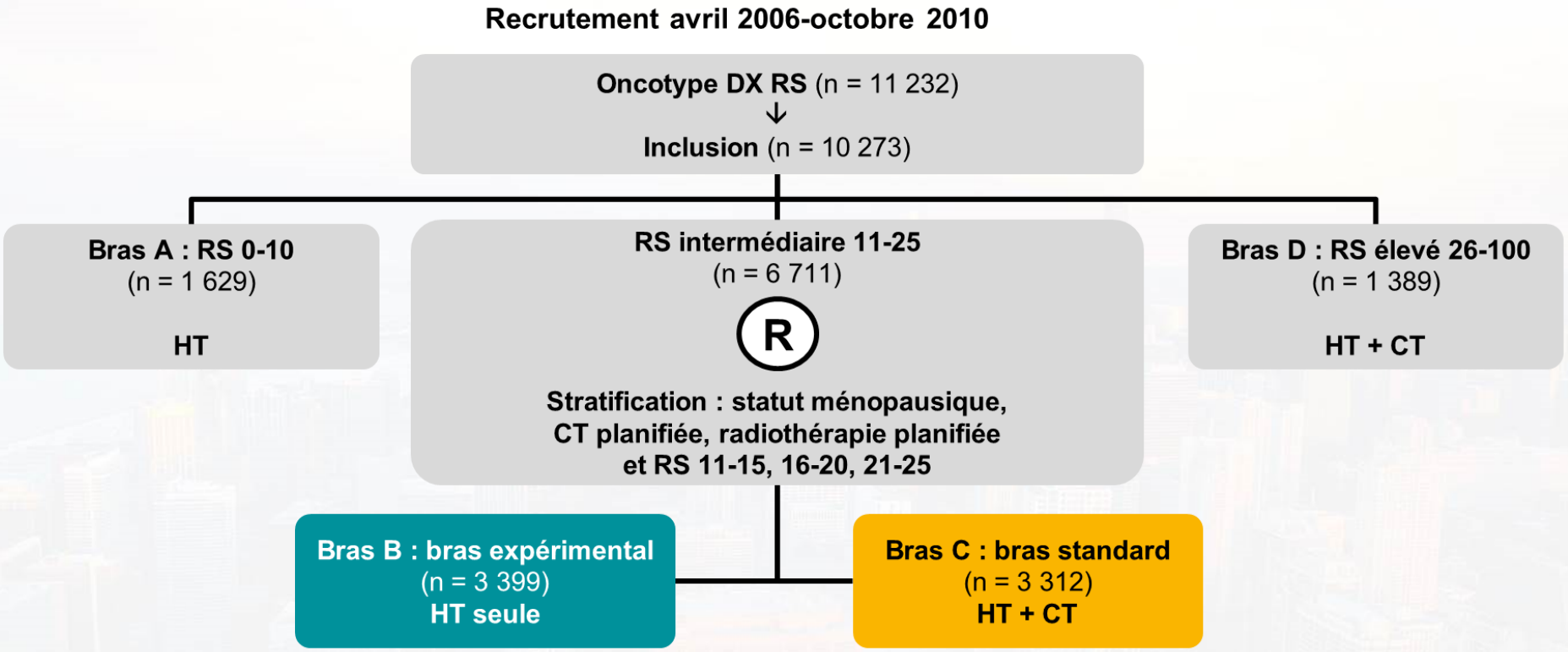






TAILORx *(1)*

- Essai clinique de phase III ayant inclus 10 273 femmes atteintes d'un cancer du sein au stade précoce avec RH+, HER2–, sans envahissement ganglionnaire



➔ Critère principal
- *Recurrence Score* (RS) 11-25 : survie sans maladie invasive (IDFS)
- *Recurrence Score* (RS) 0-10 : intervalle sans récidive à distance (DRFI)

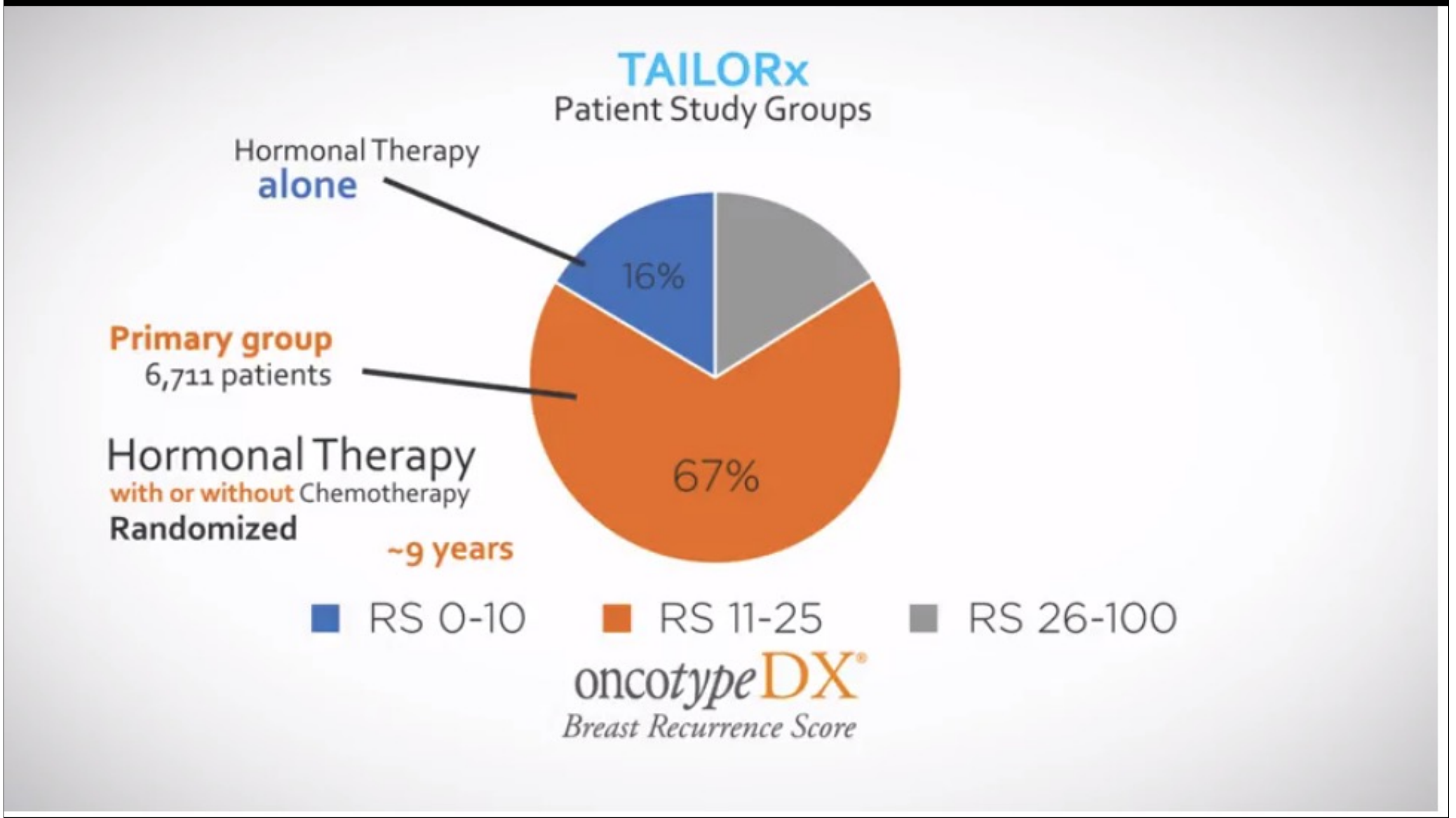
Congrès américain d'oncologie clinique 2018 - D'après Sparano JA et al., abstr. LBA1, actualisé

TailoRx Randomized Population

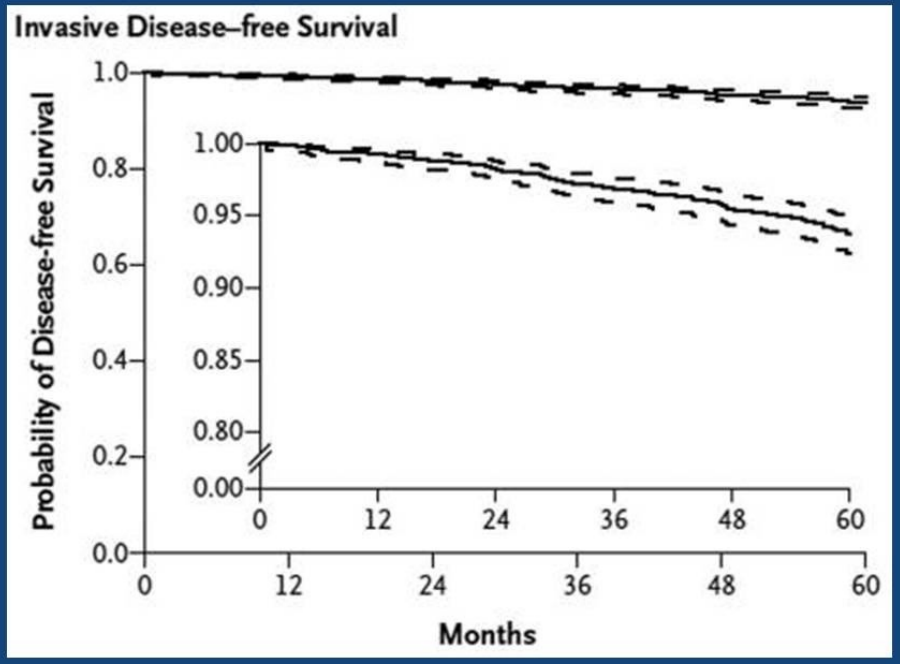
Prognostic Factor	TailoRx Population
Median age	55 (1/3 premenopausal, none > 75)
Median tumor size	1.5 cm (IQR 1.2 - 2.0 cm)
Grade	57% grade 2

~ 74% clinical low risk as defined in MINDACT

Sparano J et al, ASCO 2018


TAILORx
Patient Study Groups
Hormonal Therapy
alone
16%
Primary group
6,711 patients
Hormonal Therapy
with or without Chemotherapy
Randomized
~9 years
67%
RS 0-10
RS 11-25
RS 26-100
oncotypeDX®
Breast Recurrence Score

What We Knew Already:
RS < 11 has Great Prognosis with ET alone

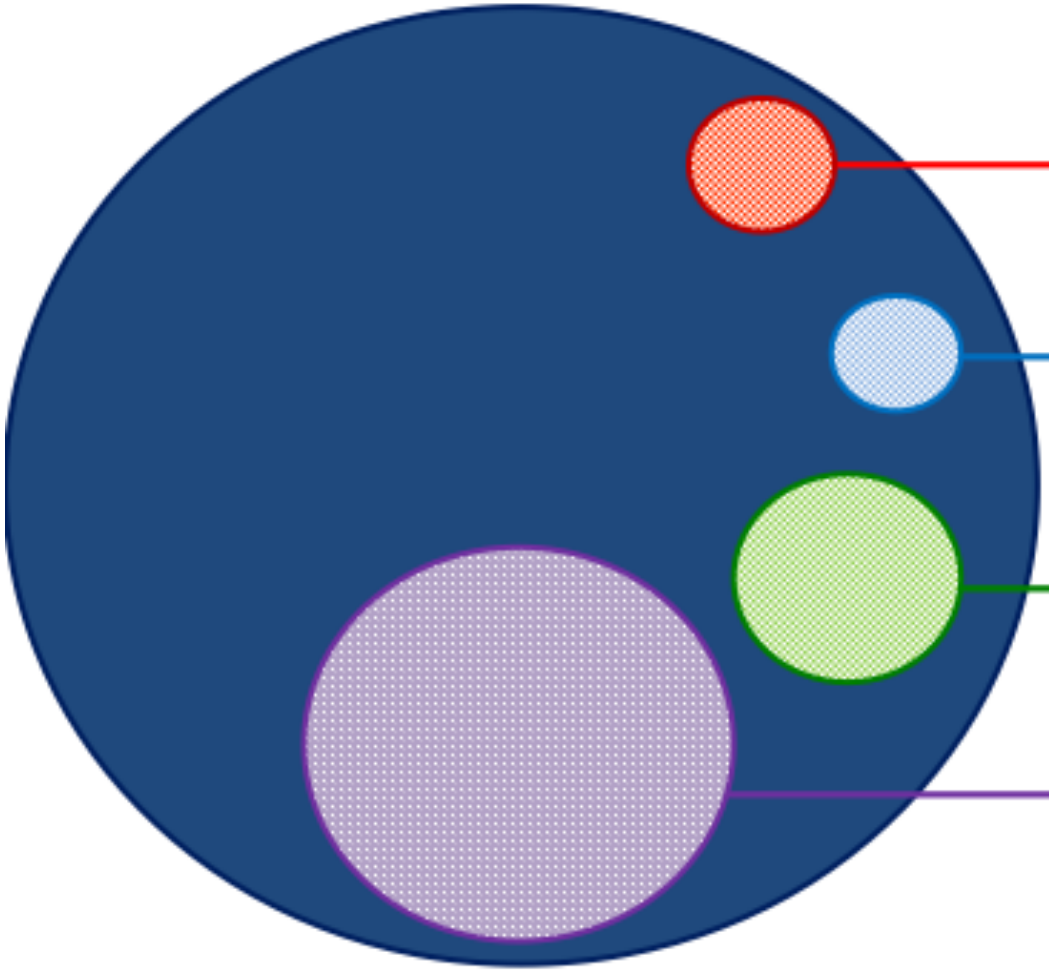


At 9 year followup

97% distant metastasis-free

Sparano J et al, NEJM 2015; ASCO 2018

TAILORx: RS 0-10
N=1626 / 88 events at median follow-up of 69 months



Rate of freedom from recurrence at distant site : 99.3% (95% ci: 98.7-99.6)

Distant recurrences N=10

Locoregional recurrences N=8

Contralateral BC (invasive) N=15

Other primary cancers N=43

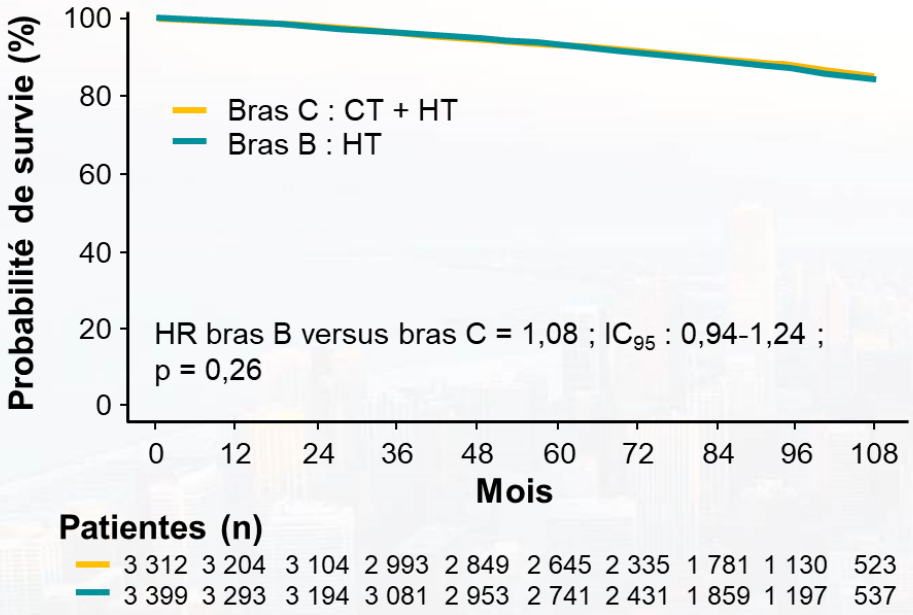
30 deaths (12 w/o cancer)

Sparano J.A. et al, N Engl J Med, Nov 19, 2015

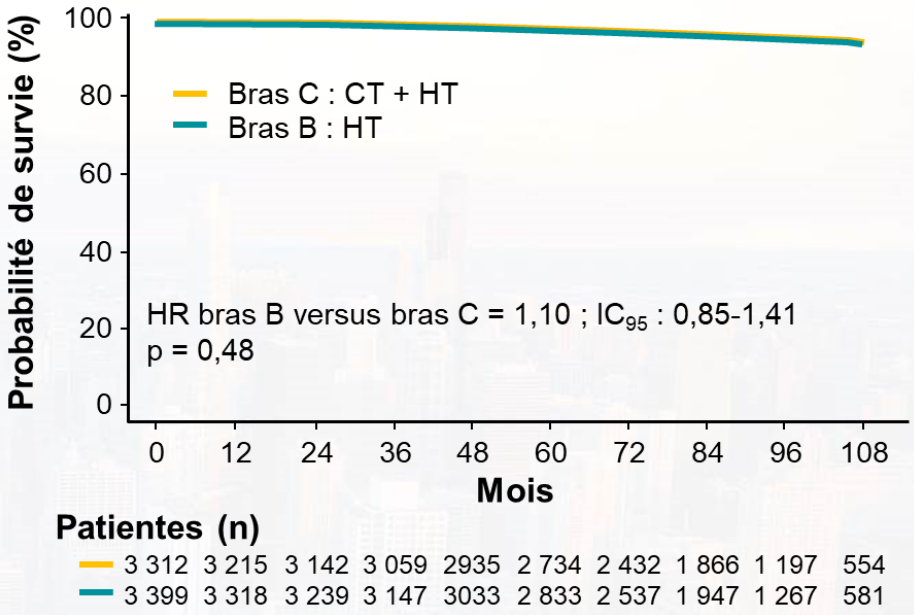
TAILORx *(2)*

Résultats groupe RS 11-25 (bras B et C)

Critère principal
Survie sans maladie invasive



Critère secondaire
Intervalle sans rechute à distance



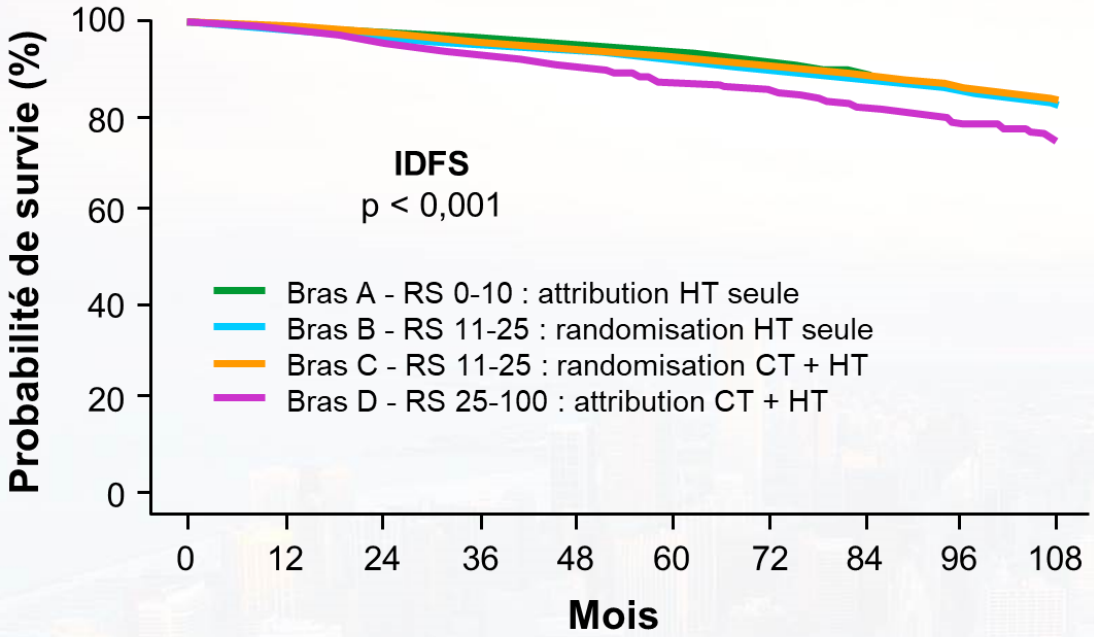
➔ **836 événements (IDFS) après un suivi médian de 7,5 ans, incluant 338 (40,3 %) récidives, dont 199 (23,8 %) à distance**

➔ **HT seule non inférieure à HT + CT**

Congrès américain d'oncologie clinique 2018 - D'après Sparano JA et al., abstr. LBA1, actualisé

TAILORx *(3)*

Résultats population en ITT : tous les bras (A, B, C et D)



Patientes (n)

1 619	1 568	1 523	1 470	1 406	1 310	1 153	867	511	213
3 399	3 293	3 194	3 081	2 953	2 741	2 431	1 859	1 197	537
3 312	3 204	3 104	2 993	2 849	2 645	2 335	1 781	1 130	523
1 389	1 291	1 174	1 090	986	617	463	329	187	77

Survie sans maladie invasive (IDFS)
Sans récidive à distance (DRFI)

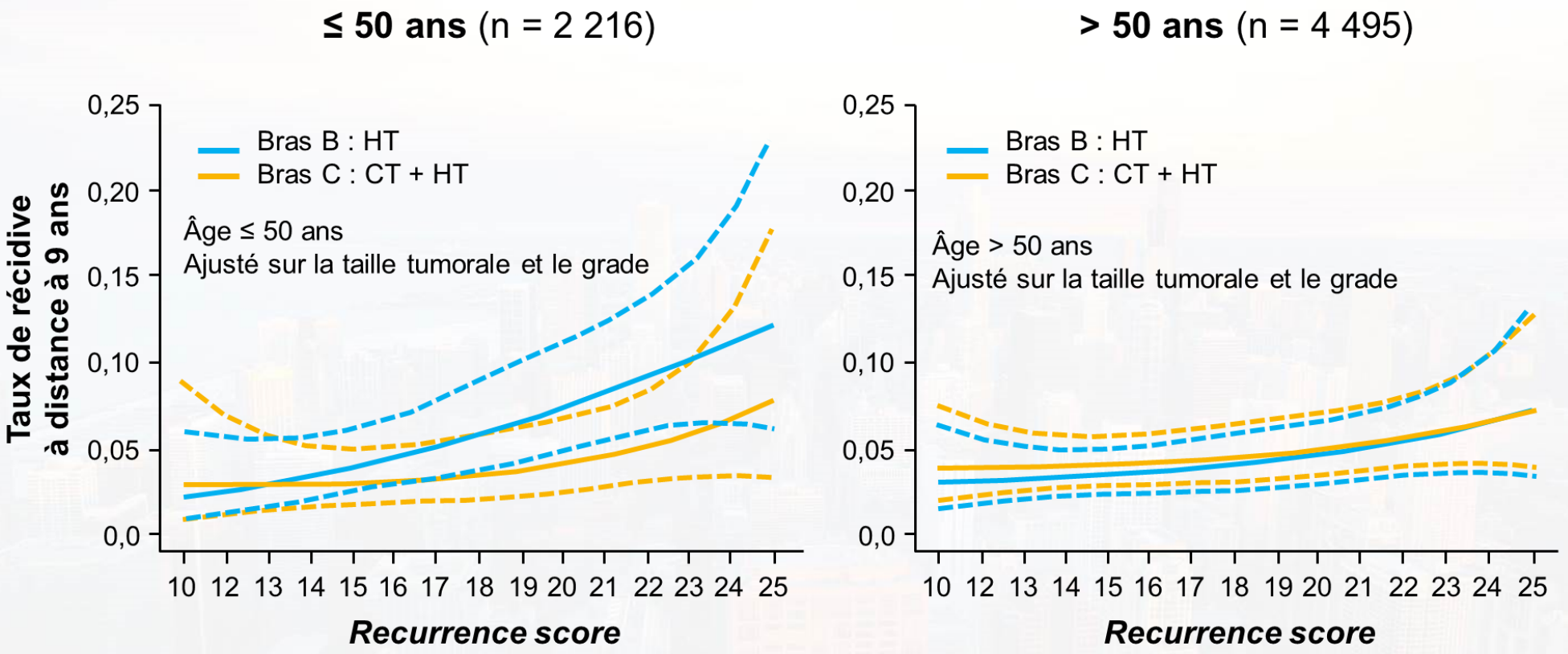
Taux d'événements à 9 ans

- **RS 0-10 (bras A)**
  - 3 % de récidive à distance avec HT seule
- **RS 11-25 (bras B et C)**
  - 5 % de taux de récidive à distance
  - ≤ 1 % de différence pour tous les critères d'évaluation
    - IDFS (83,3 versus 84,3 %)
    - DRFI (94,5 versus 95,0 %)
    - Intervalle sans rechute (92,2 versus 92,9 %)
    - SG (93,9 versus 93,8 %)
- **RS 26-100 (bras D)**
  - 13 % de récidive à distance malgré CT + HT

Congrès américain d'oncologie clinique 2018 - D'après Sparano JA et al., abstr. LBA1, actualisé

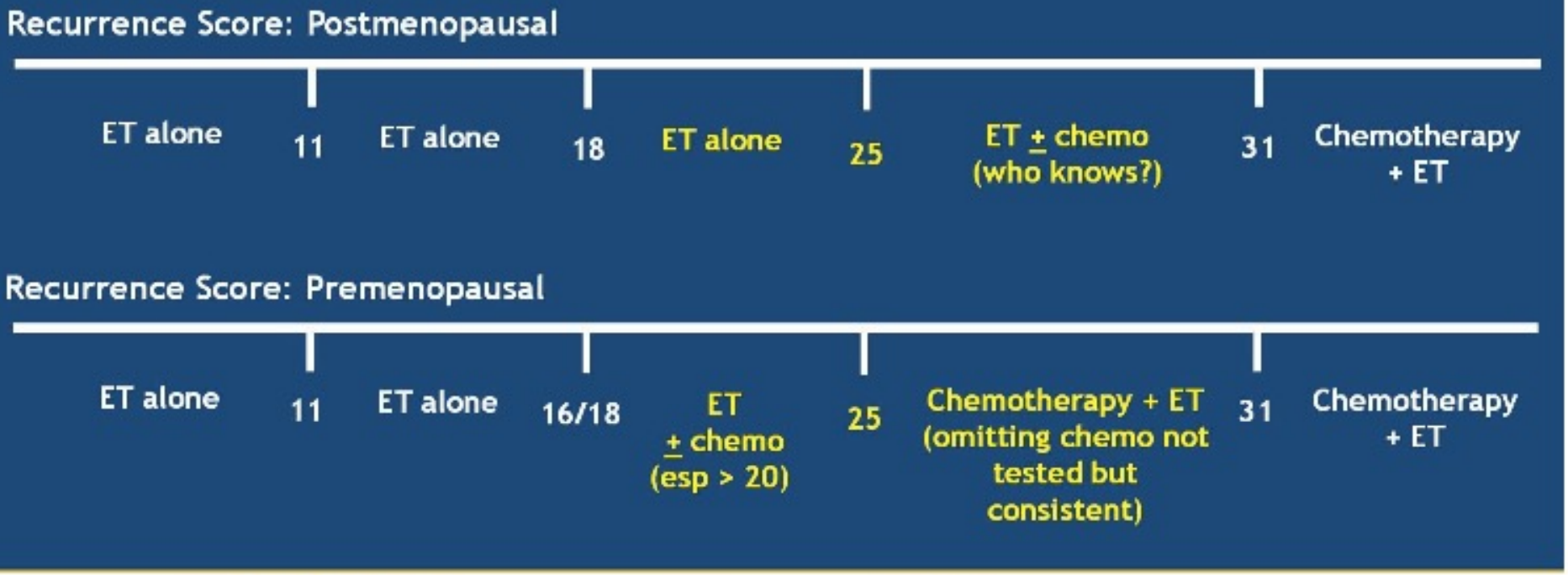
TAILORx *(4)*

Association entre RS 11-25 et taux de récidive à 9 ans en fonction du bras de traitement stratifié selon l'âge (≤ 50 ans ou > 50 ans)



Congrès américain d'oncologie clinique 2018 - D'après Sparano JA et al., abstr. LBA1, actualisé

How Does This Affect Practice Tomorrow? (for node-negative patients appropriate for chemo)



Nouvelle classification pronostique du TNM

(AJCC 8ème édition, 2017, applicable USA dès 1er janvier 2018)

1) Classification TNM
« anatomique » classique

2) **Classification TNM**
« biologique intrinsèque »

- grade histologique
- statut RE, RP, HER2
- signature moléculaire

Breast Cancer—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

CHANGE	DETAILS OF CHANGE	LEVEL OF EVIDENCE
Inclusion of multigene panels (when available) as stage modifiers—21-gene recurrence score (Oncotype Dx)	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 21-gene (Oncotype Dx) recurrence score less than 11, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0M0, and the tumor is staged using the AJCC prognostic stage group table as stage I.	I
Inclusion of multigene panels (when available) as stage modifiers—Mammaprint	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a Mammaprint low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0M0.	II
Inclusion of multigene panels (when available) as stage modifiers—EndoPredict	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 12-gene (EndoPredict) low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0M0.	II
Inclusion of multigene panels (when available) as stage modifiers—PAM50 (Prosigna)	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a PAM50 risk-of-recurrence score in the low range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0M0.	II
Inclusion of multigene panels (when available) as stage modifiers—Breast Cancer Index	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a Breast Cancer Index in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0M0.	II

Abbreviations: AJCC, American Joint Committee on Cancer; PAM50, prediction analysis of microarray 50.

The Oncotype DX® Assay
The Only Multi-gene Assay Incorporated into all Major Guidelines to Predict Adjuvant Chemotherapy Benefit in ER+, HER2- EBC

NCCN Guidelines® > 0.5 cm, node negative, N1mi	Quantifies risk of recurrence as a continuous variable and predicts responsiveness to both tamoxifen and chemotherapy[1]
ASCO® Guidelines Node negative	Predicts the risk of recurrence and may be used to identify patients likely to benefit from tamoxifen or chemotherapy[2]
ESMO Node negative	Provides additional prognostic and/or predictive information to complement pathology assessment and to predict response to adjuvant chemotherapy[4]
St Gallen Consensus Node negative, node positive	Provides not only prognostic but also predictive information regarding the utility of cytotoxic therapy in addition to endocrine therapy[3]
NICE Node negative	Recommended as an option for guidance of chemotherapy decisions in patients at intermediate risk* of distant recurrence[4]

1 NCCN Practice Guidelines in Oncology. V.3.2013.
2 Harris L, et al. *J Clin Oncol.* 2007.
3 Goldhirsch A, et al. *Ann Oncol.* 2013.
4 NICE Diagnostics Guidance 2013.

*Intermediate risk of distant recurrence is defined as NPI score ≥ 3.4 or at intermediate risk by other decision making tools or protocols

Question n°1 : Quelles indications de prescription / conditions de prescription ?

Affirmation

(gr UNICANCER)

Tumeurs luminales RE+ HER2 neg, avec incertitude sur l'indication de chimiothérapie`

Prescription en RCP

- Grade 1: T2 N0 ou 1-3 N+
- Grade 2 < 2 cm et :
  - ✓ N0 mais avec prolifération élevée (Ki67 >20%) or emboles
  - ✓ Ou 1-3 N+
- Grade 2 : 2.1-5 cm, N0
- Grade 3: 1-2 cm, N0

Question n°4 : Quelle prise en charge financière ?

Affirmation

ACCORD / DESACCORD

RIHN : 1er avril 2016

NEXT	Demande d'autorisation relative à des recherches [illegible]	[illegible]	[illegible]	[illegible]

http://social-sante.gouv.fr/systeme-de-sante-et-medico-social/recherche-et-innovation/actes-HN

- Li-RIHN pour les tests Prosigna et Endopredict
- Remontées de données nationales annuelles
  - ✓ENDPREDICT oui
  - ✓PROSIGNA? Oncotype Dx ?, Mammaprint?
- Autosaisine de l'HAS publiée le 1er Mars 2017

De nouvelles données de suivi à long terme, présentées lors du 16ème Congrès international sur le cancer du sein de St-Gallen renforcent le paradigme de traitement établi par TAILORx et l'utilisation en tant que standard of care du test Oncotype DX Breast Recurrence Score®

Patients with low Recurrence Score results can avoid chemotherapy

Several separate studies, with a total of more than 63,000 patients, found that patients with a low Recurrence Score result may be effectively treated with hormonal therapy alone and safely spared chemotherapy.[8-15] Four key studies are described below. Download a detailed summary of all four studies (PDF).

TAILORx Trial pN0	SEER Study pN0-pN1	Clalit Study pN0, pN1mi	WSG PlanB Trial pN0-pN1	
1,626 Patients	> 44,500 Patients	2,028 Patients	2,642 Patients	= > 50K Patients
Recurrence Score result < 11	Recurrence Score result < 18	Recurrence Score result < 18	Recurrence Score result ≤ 11	
5-year distant recurrence-free survival rate of > 99%	5-year breast cancer-specific survival rate of > 99%	5-year distant recurrence-free survival and breast cancer-specific survival rates of > 99%	5-year disease-free survival rate of 94%	

- ESSAI PONDx UK 582 PATIENTS N+
- AVANT ONCOTYPE CHIMIO RECOMMANDEE DANS 70% 407 patients
- APRES ONCOTYPE TX DE CT DE 27.7 %
- 66% EVITENT CT AVES TEST
- ONCOTYPE A IDENTIFIE 23 PATIENTS QUI ETAIENT PREVUS POUR HT QUI RECOIVENT CT

NICE Expands Recommendation for the Oncotype DX Breast Recurrence Score Test to More Patients with Early-Stage Breast Cancer Within the United Kingdom[4]

Oncotype Dx

(Genomic Health)

RXPONDER (2011-X)

(SWOG S1007)

Soutenu par SWOG/NCI

NCT01272037

Utilité clinique du test sur la valeur prédictive d'efficacité en vue d'une désescalade de CTA.

Tumeurs RO+/HER2- de stade précoce ou localement avancé (pT1-pT4 sauf inflammatoire), pN1a.

Inclusions : 10 000

Analyse finale prévue en 2016 puis reportée à 2022

Clinical Risk is not validated to predict chemotherapy benefit, hence would lead to over- and under-treatment

		Oncotype DX Recurrence Score®		
		RS 0-10	RS 11-25	RS 26-100
Clinical risk*	Low (n=6615)	18%	73%	9%
	High (n=2812)	12%	60%	27%

60% of patients with high clinical risk had RS result 11-25 and would have been overtreated by chemo

9% of patients with low clinical risk had RS result 26-100 and would have been undertreated

Sparano et al. *N Engl J Med* 2018

INSTITUT JULES BORDET INSTITUUT

ULB iris

Intégration de catégories cliniques

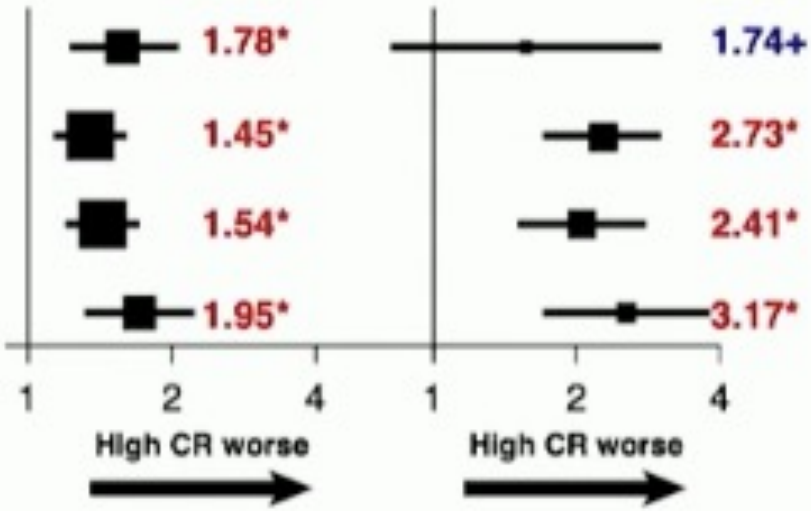
- **Background: Rationale for integrating Genomic and Clinical Risk in Early Breast Cancer**
- **Genomic risk – 21 gene recurrence score (RS) in HR+, HER2- early breast cancer**
  - Complementary prognotic information to pathologic features
    - Tumor size, grade, and nodal status
  - Predictive of large chemo benefit (RS > 25) or lack thereof (RS < 25)
    - 3-way interaction – age, RS,and chemotherapy – resulting in an absolute chemo benefit in woman < 50 years & RS 16-20 (2%) or 21-25 (7%)
- **Clinical risk – pathologic features – tumor size, grade, and nodal status**
  - Prognotic – but doesn't correlate well with RS
- **Integration of genomic and clinical risk**
  - Potential for greater precision in prognosis & guiding use of adjuvant therapy

Sparano J et al, J Clin Oncol 37, 2019 (suppl; abstr 503)

TailorX: 70% risque clinique bas , 30% risque clinique élevé

- **Results: Impact of Clinical Risk (CR) on Prognosis by RS group (N=9427) 30% clinical high risk & 70% clinical low risk**

Grouped by RS	Total #/#IDFS/DR events
All Patients (n=9427)	
RS <= 10: Endocrine Therapy	1572/176/30
RS 11-25: Endocrine Therapy	3282/422/127
RS 11-25: Chemoendocrine Therapy	3214/389/113
RS>25: Chemoendocrine Therapy	1359/184/96



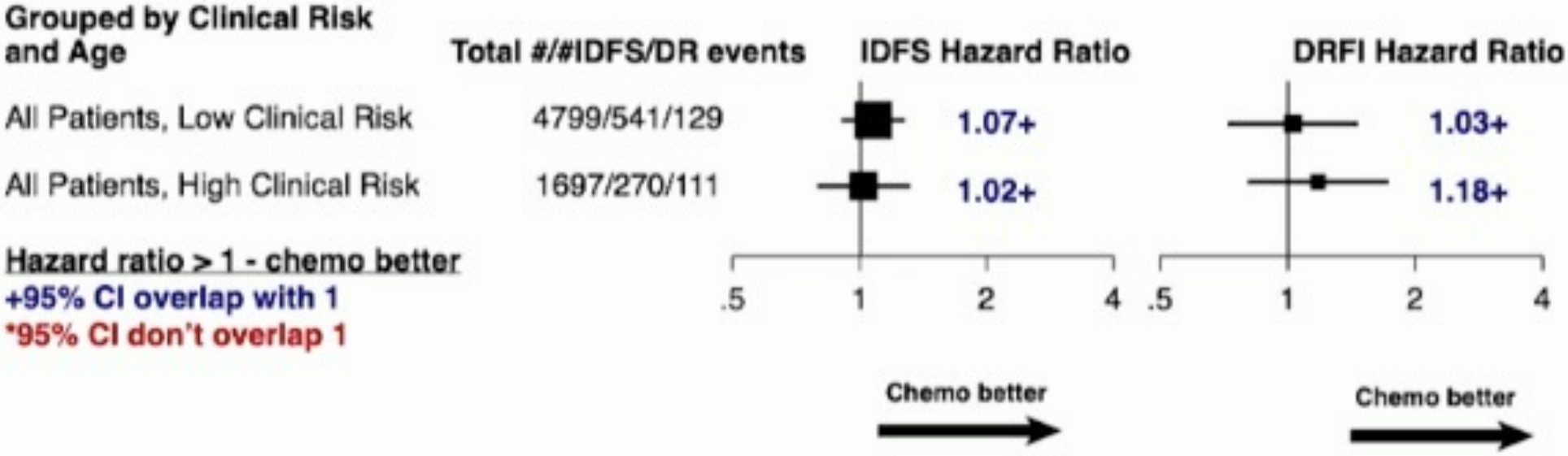
Multivariate model for distant recurrence in RS 11-25 group:
(N=6496 cases and 240 distant recurrences):
- **Clinical risk: HR for high vs. low risk 2.42, p<0.001**
- **Continuous RS: HR 1.08, p<0.001 (HR for a 1 point higher RS)**

Hazard ratio > 1 - high clinical risk worse
+95% CI overlap 1
***95% CI don't overlap 1**

Sparano J et al, J Clin Oncol 37, 2019 (suppl; abstr 503)

Prédiction du bénéfice de la chimiothérapie? Pas dans la population globale de l'essai

- **Results: Impact of Clinical Risk (CR) on Prediction of Chemotherapy Benefit by Age in RS 11-25 Group (ET vs. Chemo +ET)**



Sparano J et al, J Clin Oncol 37, 2019 (suppl; abstr 503)

Oui, mais

- **Main Results (2): Absolute Differences in 9-year Distant Recurrence Rate by Clinical Risk Stratified by Age and RS**

RS	Treatment	Absolute Risk Difference : High vs. Low Clinical Risk	
		Age > 50	Age ≤ 50
0-10	ET	Δ +4.9 (±SE 3.5%)	Δ -1.8% (±SE 0.9%)
11-25	ET	Δ +5.8% (±SE 2.0%)	Δ +7.6% (±SE 2.6%)
	Chemo-ET	Δ +4.3% (±SE 1.6%)	Δ +2.2% (±SE 2.1%)
26-100	Chemo-ET	Δ =12.8% (±SE 4.5%)	Δ +9.0% (±SE 4.1%)

Sparano J et al, J Clin Oncol 37, 2019 (suppl; abstr 503)

Risque de rechute à distance

- **Results: Absolute Differences in Distant Recurrence Rates by Chemo Use in Women ≤ 50 yrs & RS 16-25 Stratified by RS and Clinical Risk**

	Estimated Absolute Chemo Benefit Not Stratified by Clinical Risk
RS 16-20 (N=886)	Δ +1.6% (±SE 1.9%)
RS 21-25 (N=476)	Δ +6.5% (+SE 3.7%)

Sparano J et al, J Clin Oncol 37, 2019 (suppl; abstr 503)

Implication: l'intégration des catégories cliniques permet d'améliorer les décisions

- **Interaction between RS and age is exploratory, needs to be interpreted with caution**
  - Women with a RS >25 regardless of age: chemo-endocrine therapy
  - Women <50 with a RS 16-25
    - May offer chemo-endocrine therapy (TAILORx exploratory analysis)[1]
    - The majority of women <50 in TAILORx received tamoxifen alone:
    - Would they receive similar benefits from ovarian suppression and tamoxifen/AI instead of chemo-endocrine therapy?
    - May offer ovarian suppression and tamoxifen/AI (SOFT/TEXT)[2]
- **Rich resource for new explorations: biomarkers, models, machine learning**

[1]Andre F et al. JCO 2019 ; [2]Burstein H et al. JCO 2016 ; Steams V, Discussant Asco meeting 2019

MERCI DE VOTRE ECOUTE

ANALYSE EXPLORATOIRE AVEC RS ENTRE 16 ET 25 **70 % DES TUMEURS DE TAILOR SONT DE BAS RISQUE CLINIQUE AU SENS DE LA DEFINITION DE MAMMAPRINT TAILOR N A PAS REPONDU DEFINITIVEMENT A LA LA QUESTION POUR LES RISQUES INTERMEDIAIRES .LE PROBLEME N EST PAS RESOLU**

RS EST PASSE DE 18 A 11 DANS UNE POPULATION A BON PRONOSTIC

INTEGRATION DES PARAMETRES ANATOMO/ CLINIQUES AVEC LES PARAMETRES MOLECULAIRES AMELIORENT LES ESTIMATIONS DU PRONOSTIC = RSPC INTEGRANT AGE TAILLE GRADE ET LE TYPE DE TRAITEMENT HORMONAL DEFINISSANT UN SCORE PLUS PREDICTIF

28% DES PATIENTS QUI AVAIENT UN SCORE DE 18 a 30 RESTAIENT AU MEME SCORE 55% ETAIENT DOWN STAGES RECLASSES EN BAS RISQUE

ENDOPREDICT PROSIGNA INTEGRENT LA TAILLE TUMORALE LE GRADE AU RISQUE MOLECULAIRE

LE SOUS GROUPE INF A 50 ANS RS SUP A 15 NON PRE PLANIFIE ETUDE RETROSPECTTIF RECREE DES SOUS GROUPES

ONCOTYPE SEUL PAS SUFISANT DANS LES FAIBLES RISQUES

AGE SEUL NE PEUT PAS ETRE SEUL UN DRIVER

LES STADES I RH + PAS DE CHIMIO

STADES II SIGNATURES AIDE A LA DECISION IMPORTANCE D INTEGRER DES FACTEURS CLINIQUES AUX FACTEURS MOLECULAIRES